L6 ANSWER 1 OF 1 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN

ACCESSION NUMBER: 1998369739 EMBASE
TITLE: Novel therapeutic strategies for the treatment of Type 2 diabetes.
AUTHOR: Perfetti R.; Barnett P.S.; Mathur R.; Egan J.M.
CORPORATE SOURCE: Dr. R. Perfetti, Division of Endocrinology Metabolism, Department of Medicine, Cedars-Sinai Medical Center, 8700 Beverly Blvd., Los Angeles, CA 90048, United States
SOURCE: Diabetes/Metabolism Reviews, (1998) 14/3 (207-225).
Refs: 126
ISSN: 0742-4221 CODEN: DMREEG
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 003 Endocrinology
006 Internal Medicine
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Diabetes mellitus is the most common endocrine disease, accounting for over 200 million people affected worldwide. It is characterized by a lack of insulin secretion and/or increased cellular resistance to insulin, resulting in hyperglycemia and other metabolic disturbances. People with diabetes suffer from increased morbidity and premature mortality related to cardiovascular, microvascular and neuropathic complications. The Diabetes Control and Complication Trial (DCCT) has convincingly demonstrated the relationship of hyperglycemia to the development and progression of complications and showed that improved glycemic control reduced these complications. Although the DCCT exclusively studied patients with Type 1 diabetes, there is ample evidence to support the belief that the same relationship between metabolic control and clinical outcome exists in patients with Type 2 diabetes. Therefore, a major effort should be made to develop and implement more effective treatment regimes. This article reviews those novel drugs that have been recently introduced for the management of Type 2 diabetes, or that have reached an advanced level of study and will soon be proposed for preliminary clinical trials. They include: (i) compounds that promote the synthesis/secretion of insulin by the β-cell; (ii) inhibitors of the α-glucosidase activity of the small intestine; (iii) substances that enhance the action of insulin at the level of the target tissues; and (iv) inhibitors of free fatty acid oxidation.

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=> s mitiglinide
L1          36 MITIGLINIDE

=> s l1 and (inflammatory or inflammation or neuropathy or neuropathies or pain)
L2           0 L1 AND (INFLAMMATORY OR INFLAMMATION OR NEUROPATHY OR NEUROPATHI
               ES OR PAIN)

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PROCESSING COMPLETED FOR L1
L3          24 DUP REM L1 (12 DUPLICATES REMOVED)

=> focus
PROCESSING COMPLETED FOR L3
L4          24 FOCUS L3 1-

=> d ibib abs 1-24

L4   ANSWER 1 OF 24     MEDLINE on STN
ACCESSION NUMBER:    2001689244      MEDLINE
DOCUMENT NUMBER:     PubMed ID: 11716850
TITLE:               The effects of mitiglinide (KAD-1229), a new
                     anti-diabetic drug, on ATP-sensitive K+ channels and
                     insulin secretion: comparison with the sulfonylureas and
                     nateglinide.
AUTHOR:              Sunaga Y; Gonoi T; Shibasaki T; Ichikawa K; Kusama H; Yano
                     H; Seino S
CORPORATE SOURCE:    Department of Cellular and Molecular Medicine, Graduate
                     School of Medicine, Chiba University 1-8-1 Inohana,
                     Chuo-ku, 260-8670, Chiba, Japan.
SOURCE:              European journal of pharmacology, (2001 Nov 9) 431 (1)
                     119-25.
                     Journal code: 1254354. ISSN: 0014-2999.
PUB. COUNTRY:        Netherlands
DOCUMENT TYPE:       Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:            English
FILE SEGMENT:        Priority Journals
ENTRY MONTH:         200201
ENTRY DATE:          Entered STN: 20011211
                     Last Updated on STN: 20020125
                     Entered Medline: 20020111
AB   Mitiglinide (KAD-1229), a new anti-diabetic drug, is thought to
     stimulate insulin secretion by closing the ATP-sensitive K+ (K(ATP))
     channels in pancreatic beta-cells. However, its selectivity for the
     various K(ATP) channels is not known. In this study, we examined the
     effects of mitiglinide on various cloned K(ATP) channels
     (Kir6.2/SUR1, Kir6.2/SUR2A, and Kir6.2/SUR2B) reconstituted in COS-1
     cells, and compared them to another meglitinide-related compound,
     nateglinide. Patch-clamp analysis using inside-out recording
     configuration showed that mitiglinide inhibits the Kir6.2/SUR1
     channel currents in a dose-dependent manner (IC50 value, 100 nM) but does
     not significantly inhibit either Kir6.2/SUR2A or Kir6.2/SUR2B channel
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currents even at high doses (more than 10 microM). Nateglinide inhibits Kir6.2/SUR1 and Kir6.2/SUR2B channels at 100 nM, and inhibits Kir6.2/SUR2A channels at high concentrations (1 microM). Binding experiments on **mitiglinide**, nateglinide, and repaglinide to SUR1 expressed in COS-1 cells revealed that they inhibit the binding of [3H]glibenclamide to SUR1 (IC50 values: **mitiglinide**, 280 nM; nateglinide, 8 microM; repaglinide, 1.6 microM), suggesting that they all share a glibenclamide binding site. The insulin responses to glucose, **mitiglinide**, tolbutamide, and glibenclamide in MIN6 cells after chronic **mitiglinide**, nateglinide, or repaglinide treatment were comparable to those after chronic tolbutamide and glibenclamide treatment. These results indicate that, similar to the sulfonylureas, **mitiglinide** is highly specific to the Kir6.2/SUR1 complex, i.e., the pancreatic beta-cell K(ATP) channel, and suggest that **mitiglinide** may be a clinically useful anti-diabetic drug.

L4 ANSWER 2 OF 24 EMBASE
on STN

ACCESSION NUMBER: 2003484444 EMBASE
TITLE: Pharmacology of the Meglitinide Analogs: New Treatment Options for Type 2 Diabetes Mellitus.
AUTHOR: Malaisse W.J.
CORPORATE SOURCE: Prof. W.J. Malaisse, Lab. of Experimental Hormonology, Brussels Free University, 808 Route de Lennik, Brussels, B-1070, Belgium. malaisse@ulb.ac.be
SOURCE: Treatments in Endocrinology, (2003) 2/6 (401-414).
Refs: 83
ISSN: 1175-6349 CODEN: TERNAN
COUNTRY: New Zealand
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The expression meglitinide analogs was introduced in 1995 to cover new molecules proposed as non-sulfonylurea insulinotropic agents and displaying structural analogy with meglitinide, such as repaglinide, nateglinide, and **mitiglinide**. Meglitinide analogs display, as judged by conformation analysis, a U-shaped configuration similar to that of antihyperglycemic sulfonylureas such as glibenclamide (glyburide) and glimepiride. In rat pancreatic islets incubated in the presence of 7.0 mmol/L D-glucose, repaglinide and **mitiglinide** demonstrate comparable concentration-response relationships for stimulation of insulin release, with a threshold value <10 nmol/L and a maximal secretory response at about 10 nmol/L. Several findings indicate that meglitinide analogs provoke the closing of adenosine triphosphate-sensitive potassium channels, with subsequent gating of voltage-sensitive calcium channels. The effects of meglitinide analogs upon the binding of [(3)H]glibenclamide to islet cells membranes reinforces this concept. At variance, however, with other meglitinide analogs, the ionic and secretory response to repaglinide (10 μmol/L) is not rapidly reversible in perifused rat islets. In experiments conducted in vivo in control and diabetic rats, repaglinide provokes a greater and more rapid increase in plasma insulin concentration and an earlier fall in glycemia than glibenclamide or glimepiride. Onset of effect is also more rapid and duration of effect shorter with nateglinide versus glibenclamide. In clinical studies, single or repeated daily administration of repaglinide increased plasma insulin concentration in a dose-dependent manner, with an incremental peak reached about 2 hours after repaglinide intake. Plasma concentrations of repaglinide are about 5.0 μg/L 2-2.5 hours after oral intake of the drug. Despite the slow reversibility of repaglinide action in vitro, this drug offers advantages over glibenclamide in terms of the possible occurrence of hypoglycemia if a meal is missed. In volunteers receiving a single oral dose of nateglinide (120mg) 10 minutes before a standardized

800 Kcal breakfast, the plasma insulin concentration was higher 5, 10, and 20 minutes after meal intake than when they received a single dose of repaglinide (0.5 or 2.0mg) or placebo 10 minutes before breakfast. Peak plasma concentrations of nateglinide were reached within 2 hours in most volunteers. Peak plasma concentrations of **mitiglinide** were reached 30 minutes after a single oral dose in a representative volunteer. **Mitiglinide** significantly suppressed meal-induced elevations in blood glucose concentrations in a study of patients with type 2 diabetes. In conclusion, two obvious differences among these meglitinide analogs should be underlined. First, on a molar basis, nateglinide is somewhat less potent than repaglinide or **mitiglinide**, as an insulinotropic agent. The maximal secretory responses evoked by these three meglitinide analogs are, however, identical to one another. Secondly, and as already mentioned, the functional effects of nateglinide and **mitiglinide** are more rapidly reversible than those of repaglinide, for instance in perifused rat islets. The meglitinide analogs offer the advantage over the long-acting antihyperglycemic sulfonylurea glibenclamide of minimizing the risk of undesirable hypoglycemia.

L4 ANSWER 3 OF 24 MEDLINE on STN
ACCESSION NUMBER: 2001260288 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11264248
TITLE: Effects of **mitiglinide** (S 21403) on Kir6.2/SUR1, Kir6.2/SUR2A and Kir6.2/SUR2B types of ATP-sensitive potassium channel.
AUTHOR: Reimann F; Proks P; Ashcroft F M
CORPORATE SOURCE: University Laboratory of Physiology, Parks Road, Oxford OX1 3PT.
SOURCE: British journal of pharmacology, (2001 Apr) 132 (7) 1542-8. Journal code: 7502536. ISSN: 0007-1188.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200105
ENTRY DATE: Entered STN: 20010521
Last Updated on STN: 20010521
Entered Medline: 20010517

AB 1. We have investigated the mechanism of action of the novel anti-diabetic agent **mitiglinide** (S 21403) on Kir6.2/SUR1, Kir6.2/SUR2A and Kir6.2/SUR2B types of ATP-sensitive potassium (K(ATP)) channel. These possess a common pore-forming subunit, Kir6.2, and different regulatory sulphonylurea receptor (SUR) subunits. It is believed that they correspond to native K(ATP) channels in pancreatic beta-cells, heart and non-vascular smooth muscle, respectively. 2. Kir6.2 was coexpressed with SUR1, SUR2A or SUR2B in Xenopus oocytes and macroscopic currents were recorded in giant inside-out membrane patches. **Mitiglinide** was added to the intracellular membrane surface. 3. **Mitiglinide** inhibited Kir6.2/SUR currents at two sites: a low-affinity site on Kir6.2 and a high-affinity site on SUR. Low-affinity inhibition was similar for all three types of K(ATP) channel but high-affinity inhibition was greater for Kir6.2/SUR1 currents (IC(50), 4 nM) than for Kir6.2/SUR2A or Kir6.2/SUR2B currents (IC(50), 3 and 5 microM, respectively). 4. Inhibition of Kir6.2/SUR1 currents was only slowly reversible on the time scale of electrophysiological experiments. 5. Kir6.2/SUR1-S1237Y currents, which previously have been shown to lack high affinity tolbutamide inhibition, resembled Kir6.2/SUR2 currents in being unaffected by 100 nM but blocked by 10 microM **mitiglinide**. 6. Our results show that **mitiglinide** is a high-affinity drug that shows a 1000 fold greater affinity for the beta-cell type than the cardiac and smooth muscle types of K(ATP) channel, when measured in excised patches.

L4 ANSWER 4 OF 24 MEDLINE on STN

ACCESSION NUMBER: 1999430071 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10498841
TITLE: Inhibition of heterologously expressed cystic fibrosis transmembrane conductance regulator Cl- channels by non-sulphonylurea hypoglycaemic agents.
AUTHOR: Cai Z; Lansdell K A; Sheppard D N
CORPORATE SOURCE: Human Genetics Unit, Department of Medical Sciences, University of Edinburgh, Molecular Medicine Centre, Western General Hospital, Edinburgh EH4 2XU.
SOURCE: British journal of pharmacology, (1999 Sep) 128 (1) 108-18. Journal code: 7502536. ISSN: 0007-1188.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199911
ENTRY DATE: Entered STN: 20000111
Last Updated on STN: 20000111
Entered Medline: 19991122

AB 1. Hypoglycaemia-inducing sulphonylureas, such as glibenclamide, inhibit cystic fibrosis transmembrane conductance regulator (CFTR) Cl- channels. In search of modulators of CFTR, we investigated the effects of the non-sulphonylurea hypoglycaemic agents meglitinide, repaglinide, and **mitiglinide** (KAD-1229) on CFTR Cl- channels in excised inside-out membrane patches from C127 cells expressing wild-type human CFTR. 2. When added to the intracellular solution, meglitinide and **mitiglinide** inhibited CFTR Cl- currents with half-maximal concentrations of 164+/-19 microM and 148+/-36 microM, respectively. However, repaglinide only weakly inhibited CFTR Cl- currents. 3. To understand better how non-sulphonylurea hypoglycaemic agents inhibit CFTR, we studied single channels. Channel blockade by both meglitinide and **mitiglinide** was characterized by flickery closures and a significant decrease in open probability (Po). In contrast, repaglinide was without effect on either channel gating or Po, but caused a small decrease in single-channel current amplitude. 4. Analysis of the dwell time distributions of single channels indicated that both meglitinide and **mitiglinide** greatly decreased the open time of CFTR. **Mitiglinide**-induced channel closures were about 3-fold longer than those of meglitinide. 5. Inhibition of CFTR by meglitinide and **mitiglinide** was voltage-dependent: at positive voltages channel blockade was relieved. 6. The data demonstrate that non-sulphonylurea hypoglycaemic agents inhibit CFTR. This indicates that these agents have a wider specificity of action than previously recognized. Like glibenclamide, non-sulphonylurea hypoglycaemic agents may inhibit CFTR by occluding the channel pore and preventing Cl- permeation.

L4 ANSWER 5 OF 24 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2002:227295 BIOSIS
DOCUMENT NUMBER: PREV200200227295
TITLE: Novel hypoglycemic drug **mitiglinide** and cardiac membrane excitability.
AUTHOR(S): Zingman, L. V. [Reprint author]; Hodgson, D. [Reprint author]; Abraham, M. [Reprint author]; Alekseev, A. [Reprint author]; Terzic, A. [Reprint author]
CORPORATE SOURCE: Mayo Clinic, Rochester, MN, USA
SOURCE: Clinical Pharmacology and Therapeutics, (February, 2002) Vol. 71, No. 2, pp. P3. print.
Meeting Info.: Annual Meeting of the American Society for Clinical Pharmacology and Therapeutics. Atlanta, Georgia, USA. March 24-27, 2002. American Society for Clinical Pharmacology and Therapeutics.
CODEN: CLPTAT. ISSN: 0009-9236.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)

LANGUAGE: English
ENTRY DATE: Entered STN: 3 Apr 2002
Last Updated on STN: 3 Apr 2002

L4 ANSWER 6 OF 24 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2004068924 EMBASE
TITLE: Novel strategies for the pharmacological management of type 2 diabetes.
AUTHOR: Nourparvar A.; Bulotta A.; Di Mario U.; Perfetti R.
CORPORATE SOURCE: R. Perfetti, Div. of Endocrinology and Metabolism, Cedars-Sinai Medical Center, SSB # 290, 8723 Alden Drive, Los Angeles, CA 90048, United States. perfettir@cshs.org
SOURCE: Trends in Pharmacological Sciences, (2004) 25/2 (86-91). Refs: 61
ISSN: 0165-6147 CODEN: TPHSDY
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 003 Endocrinology
030 Pharmacology
036 Health Policy, Economics and Management
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Type 2 diabetes is characterized by high concentrations of glucose in the blood, which is caused by decreased secretion of insulin from the pancreas and decreased insulin action. This condition is prevalent worldwide and is associated with morbidity and mortality secondary to complications such as myocardial infarction, stroke and end-stage renal disease. The importance of tight control of blood glucose in either preventing or delaying the progression of complications is recognized. Currently, there are many therapeutic options to treat hyperglycemia in type 2 diabetes. However, tight control is difficult to achieve and is often associated with side-effects. Recent advances in understanding insulin secretion, action and signaling have led to the development of new pharmacological agents. In this article, we review new molecules that are promising candidates for the future management of diabetes, focusing on their mechanism of action, efficacy, safety profile and potential benefits compared with pharmacological agents that are available currently.

L4 ANSWER 7 OF 24 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2004050138 EMBASE
TITLE: World Congress of Pharmacology - XIVth Annual Meeting: New drugs I: 7-12 July 2002, San Francisco, CA, USA.
AUTHOR: Waterworth C.; Durrance A.
CORPORATE SOURCE: C. Waterworth, Current Drugs Ltd., Middlesex House, 34-42 Cleveland Street, London W1T 4LB, United Kingdom. charlotte.waterworth@current.drugs.com
SOURCE: IDrugs, (2002) 5/8 (745-748).
ISSN: 1369-7056 CODEN: IDRUFN
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 037 Drug Literature Index
029 Clinical Biochemistry
025 Hematology
030 Pharmacology
018 Cardiovascular Diseases and Cardiovascular Surgery
LANGUAGE: English

L4 ANSWER 8 OF 24 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2001:56868 BIOSIS
DOCUMENT NUMBER: PREV200100056868

TITLE: **Mitiglinide** calcium hydrate. Antidiabetic.
AUTHOR(S): Sorbera, L. A. [Reprint author]; Leeson, P. A. [Reprint author]; Castaner, R. M. [Reprint author]; Castaner, J. [Reprint author]
CORPORATE SOURCE: Prous Science, 08080, Barcelona, Spain
SOURCE: Drugs of the Future, (October, 2000) Vol. 25, No. 10, pp. 1034-1042. print.
ISSN: 0377-8282.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 24 Jan 2001
Last Updated on STN: 12 Feb 2002

L4 ANSWER 9 OF 24 MEDLINE on STN
ACCESSION NUMBER: 2003359695 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12891883
TITLE: [Meglitinide analogs: new insulinotropic agents for the treatment of non-insulin dependent diabetes]. Analogues du meglitinide: nouveaux agents insulinotropes pour le traitement du diabete non-insulinodependant.
AUTHOR: Malaisse W J
CORPORATE SOURCE: Laboratoire d'Hormonologie Experimentale, Faculte de Medecine, U.L.B.
SOURCE: Revue medicale de Bruxelles, (2003 Jun) 24 (3) 162-8. Ref: 53
Journal code: 8003474. ISSN: 0035-3639.
PUB. COUNTRY: Belgium
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: French
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200310
ENTRY DATE: Entered STN: 20030802
Last Updated on STN: 20031029
Entered Medline: 20031028

AB In 1995, several new molecules under study as potential insulinotropic agents for the treatment of non-insulindependent diabetes mellitus were identified as analogs of meglitinide, previously known as the non-sulfonylurea moiety of glibenclamide. Three of these molecules, namely repaglinide, nateglinide and **mitiglinide** are or will be soon available for administration to diabetic patients. The present report aims at reviewing both preclinical studies and clinical investigations concerning the latter three meglitinide analogs. Their insulinotropic action seems attributable, like that of hypoglycaemic sulfonylureas, to a primary effect on the ATP-sensitive K+ channels of pancreatic insulin-producing cells. These meglitinide analogs differ from one another, however, by their potency as insulinotropic agents and by the time course of their biological effects, especially in terms of the reversibility of such effects.

L4 ANSWER 10 OF 24 MEDLINE on STN
ACCESSION NUMBER: 2003345780 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12877090
TITLE: Nateglinide and **mitiglinide**.
AUTHOR: Odawara Masato
CORPORATE SOURCE: Department of Endocrinology and Metabolism, Toranomon Hospital.
SOURCE: Nippon rinsho. Japanese journal of clinical medicine, (2003 Jul) 61 (7) 1230-7. Ref: 12
Journal code: 0420546. ISSN: 0047-1852.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)

(REVIEW, TUTORIAL)
LANGUAGE: Japanese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200309
ENTRY DATE: Entered STN: 20030725
Last Updated on STN: 20030926
Entered Medline: 20030925

AB Patients with type 2 diabetes mellitus are associated with insulin resistance and/or impaired insulin secretion. Previous observations indicate that Japanese patients with type 2 diabetes tend to have impaired insulin response after glycemic load more often than Caucasian counterparts. Recently it has been reported that hyperglycemia after glucose load is itself a risk factor for the development of cardiovascular complications in the absence of elevated fasting plasma glucose. Recent observations on the association of post-challenge or post-prandial hyperglycemia with cardiovascular events suggest that lowering post-prandial plasma glucose may protect patients from developing cardiovascular diseases. Results of STOP-NIDDM trial suggest that nateglinide, which attenuates post-prandial glycemic surge in type 2 diabetes, may also be helpful for the protection against cardiovascular events. Nateglinide exerts its effects shortly after its administration and the effects continue for only about 3 hours. The patients receiving this agent rarely gain weight and develop hypoglycemia. This agent exerts hypoglycemic effects additively with alpha-gulucosidase inhibitors or metformin.

L4 ANSWER 11 OF 24 MEDLINE on STN
ACCESSION NUMBER: 2002629873 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12387051
TITLE: **Mitiglinide** (KAD-1229).
AUTHOR: Kusama Hiroshi; Shibata Nobuo
CORPORATE SOURCE: Kissei Pharmaceutical Co., Ltd.
SOURCE: Nippon rinsho. Japanese journal of clinical medicine, (2002 Sep) 60 Suppl 9 559-65. Ref: 6
Journal code: 0420546. ISSN: 0047-1852.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: Japanese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200212
ENTRY DATE: Entered STN: 20021022
Last Updated on STN: 20021227
Entered Medline: 20021224

L4 ANSWER 12 OF 24 MEDLINE on STN
ACCESSION NUMBER: 2001681821 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11728565
TITLE: Insulinotropic meglitinide analogues.
COMMENT: Comment in: Lancet. 2002 Apr 6;359(9313):1248. PubMed ID: 11955566
Comment in: Lancet. 2002 Jan 12;359(9301):166-7. PubMed ID: 11809285
AUTHOR: Dornhorst A
CORPORATE SOURCE: Department of Metabolic Medicine, Faculty of Medicine, Imperial College, Hammersmith Hospital Campus, Du Cane Road, W12 0NN, London, UK.. a.dornhorst@ic.ac.uk
SOURCE: Lancet, (2001 Nov 17) 358 (9294) 1709-16. Ref: 78
Journal code: 2985213R. ISSN: 0140-6736.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)

LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20011203
Last Updated on STN: 20020430
Entered Medline: 20011213

AB The loss of early-phase insulin secretion is an important and early event in the natural history of type 2 diabetes. Because a normal pattern of insulin secretion is essential for the effective control of postprandial metabolism, a rational basis for the development of agents that target early-phase insulin release exists. Conventional oral hypoglycaemic agents do not target, or adequately control, postprandial glycaemia. The emergence of new classes of oral agent with a more specific mode of action provides, for the first time, an opportunity to restore early-phase insulin release. One such drug class is the meglitinide analogues (repaglinide, nateglinide, and **mitiglinide**). These drugs are ideally suited for combination use with metformin. They could also prove effective in combination with a thiazolidinedione, a drug class that targets insulin resistance. Exogenous insulin is frequently required in the late management of type 2 diabetes. However, one hope for newer combinations of diabetic drugs is that the functional life of the beta cell can be extended, thereby delaying the need for insulin injections.

L4 ANSWER 13 OF 24 MEDLINE on STN
ACCESSION NUMBER: 2000280289 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10820654
TITLE: **Mitiglinide**. KAD 1229.
AUTHOR: Anonymous
SOURCE: Drugs in R&D, (1999 Aug) 2 (2) 114-5.
Journal code: 100883647. ISSN: 1174-5886.
PUB. COUNTRY: New Zealand
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200008
ENTRY DATE: Entered STN: 20000811
Last Updated on STN: 20000811
Entered Medline: 20000801

L4 ANSWER 14 OF 24 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2004004730 EMBASE
TITLE: Monograph Updates of Endocrine and Metabolic Drugs.
AUTHOR: Mealy N.E.; Bayes M.
CORPORATE SOURCE: N.E. Mealy, Prous Science, P.O. Box 540, 08080 Barcelona, Spain
SOURCE: Drugs of the Future, (2003) 28/10 (1021-1046).
ISSN: 0377-8282 CODEN: DRFUD4
COUNTRY: Spain
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 003 Endocrinology
006 Internal Medicine
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English

L4 ANSWER 15 OF 24 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2002183147 EMBASE
TITLE: Effect of KAD-1229, a novel hypoglycaemic agent, on plasma glucose levels after meal load in type 2 diabetic rats.
AUTHOR: Ichikawa K.; Yamato T.; Ojima K.; Tsuji A.; Ishikawa K.; Kusama H.; Kojima M.
CORPORATE SOURCE: K. Ichikawa, Pharmacology Laboratories, Kissei

Pharmaceutical Co. Ltd, 4365-1 Kashiwabara, Hotaka, Minamiazumi, Nagano 399-8304, Japan. kiyoshi_ichikawa@pharm.kissei.co.jp

SOURCE: Clinical and Experimental Pharmacology and Physiology, (2002) 29/5-6 (423-427). Refs: 24 ISSN: 0305-1870 CODEN: CEXPB

COUNTRY: Australia

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 003 Endocrinology
030 Pharmacology
037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

AB 1. The effects of KAD-1229 (a novel non-sulphonylurea agent), voglibose (an α-glucosidase inhibitor) and nateglinide (a non-sulphonylurea antihyperglycaemic agent) on hyperglycaemia induced by a meal load were assessed in diabetic rats. 2. KAD-1229 suppressed the increase in plasma glucose levels seen after a meal load and the area under the curve for plasma glucose levels (AUC(glucose)) up to 5 h after the meal load. 3. Voglibose also suppressed the increase in plasma glucose levels; however, a significant decrease in AUC(glucose) following voglibose was not observed. 4. Nateglinide suppressed the increase in plasma glucose levels at 30 min and 1 h after the meal load; however, plasma glucose levels was above control thereafter and the AUC(glucose) was not decreased. 5. The results indicate that KAD-1229 has an antihyperglycaemic effect and KAD-1229 is suggested to be a suitable agent for controlling post-prandial hyperglycaemia.

L4 ANSWER 16 OF 24 MEDLINE on STN

ACCESSION NUMBER: 2002739769 MEDLINE

DOCUMENT NUMBER: PubMed ID: 12450580

TITLE: Effects of S 21403 on hormone secretion from isolated rat pancreas at different glucose concentrations.

AUTHOR: Gregorio Franco; Ambrosi Franca; Boemi Massimo; Carle Flavia; Filipponi Paolo

CORPORATE SOURCE: Anti-Diabetic Unit, Medical Department E. Profili General Hospital, 60044 Fabriano, AN, Italy.. franco.gregorio@tin.it

SOURCE: European journal of pharmacology, (2002 Dec 5) 456 (1-3) 141-7. Journal code: 1254354. ISSN: 0014-2999.

PUB. COUNTRY: Netherlands

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200305

ENTRY DATE: Entered STN: 20021231
Last Updated on STN: 20030520
Entered Medline: 20030519

AB We investigated the in vitro effects of therapeutical concentrations of S 21403 (a succinic acid derivative also known as KAD 1229 and **mitiglinide**) on insulin and glucagon secretion during a metabolic stimulus (glucose rising from 5 to 8.33 mM) or at a stable 2.22 mM glucose using the isolated perfused rat pancreas model, and we compared them with the patterns of repaglinide and glibenclamide. Control perfusions were also performed. During 8.33 mM glucose, insulin release peaked to 339.12+/-22.87 microU/ml in controls. S 21403 enhanced insulin release (first peak 413.02+/-14.90 microU/ml; P<0.03 vs. controls, P=ns vs. repaglinide, P<0.005 vs. glibenclamide). Repaglinide increased glucose-induced first peak secretion to 409.33+/-20.05 microU/ml within the eighth minute (P<0.05 vs. controls, P<0.01 vs. glibenclamide). Glibenclamide did not affect the first phase of glucose-induced insulin release (peak of 338.41+/-29.79 microU/ml) but potentiated and delayed the

second phase. No drug affected glucagon release. In conclusion, S 21403 induces a faster, more physiological pattern of insulin release than the other drugs we tested.

L4 ANSWER 17 OF 24 MEDLINE on STN
ACCESSION NUMBER: 2000280282 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10820647
TITLE: Recent developments and emerging therapies for type 2 diabetes mellitus.
AUTHOR: Evans A J; Krentz A J
CORPORATE SOURCE: Department of Diabetes and Endocrinology, Southampton General Hospital, England.
SOURCE: Drugs in R&D, (1999 Aug) 2 (2) 75-94. Ref: 106
Journal code: 100883647. ISSN: 1174-5886.
PUB. COUNTRY: New Zealand
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200008
ENTRY DATE: Entered STN: 20000811
Last Updated on STN: 20000811
Entered Medline: 20000801

AB Most patients with type 2 (non-insulin-dependent) diabetes mellitus require pharmacotherapy, initially as monotherapy and subsequently in combination, as adjuncts to diet and exercise. Exogenous insulin is ultimately required in a substantial proportion, reflecting the progressive natural history of the disease. Sulphonylureas and biguanides have been employed for over 4 decades as oral antidiabetic agents, but they have a limited capacity to provide long term glycaemic control and can cause serious adverse effects. Thus, more efficacious and tolerable antidiabetic agents are required. Recent years have witnessed the introduction of agents with novel modes of action, that is, the alpha-glucosidase inhibitors acarbose and miglitol (which reduce postprandial hyperglycaemia) and the first of the thiazolidinedione insulinsensitising drugs--troglitazone and rosiglitazone. Although the former has been withdrawn in some countries due to adverse effects, another 'glitazone' pioglitazone is expected to be approved in the near future. Other recently introduced drugs include glimepiride and the meglitinide insulin secretagogue, repaglinide. Attention is also focusing increasingly on combination therapy using insulin together with sulphonylureas, metformin or troglitazone. Rapid-acting insulin analogues are now being used as alternatives to conventional insulins; their role in the management of type 2 diabetes mellitus is presently uncertain but reports of a reduced frequency of hypoglycaemia are encouraging. The development of new drugs aims to counter the principal metabolic defects of the disorder, respectively, relative insulin deficiency and insulin resistance. Novel classes of rapid-acting secretagogues under evaluation include the morphilinoguanide BTS 67582 and the meglitinides **mitiglinide** (KAD 1229) and senaglinide (A-4166). Succinate ester derivatives represent a potential novel approach to improving beta-cell function through enhancement of insulin biosynthesis and secretion. Enhancement of nutrient-induced insulin secretion is a mechanism with several putative targets within the beta-cell; potentiators of insulin secretion include glucagon-like peptide-1 and its analogues, phosphodiesterase inhibitors and the imidazoline derivative PMS 812 (S 21663). The amylin agonist pramlintide slows gastric emptying and suppression of glucagon secretion. Non-thiazolidinedione insulin-sensitising agents include the gamma-receptor agonist G 1262570X (GG 570) and D-chiro-inositol. Insulin analogues with prolonged action and inhaled insulin preparations are also under investigation. Insulin-mimetic agents include organic vanadium compounds. Whether newer agents will offer clinically relevant efficacy and tolerability advantages

over existing therapies remains to be determined.

L4 ANSWER 18 OF 24 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2004105024 EMBASE
TITLE: Clinical Pharmacokinetics of Nateglinide: A Rapidly-Absorbed, Short-Acting Insulinotropic Agent.
AUTHOR: McLeod J.F.
CORPORATE SOURCE: Dr. J.F. McLeod, Novartis Pharmaceuticals, One Health Plaza, East Hanover, NJ 07936, United States. james.mcleod@pharma.novartis.com
SOURCE: Clinical Pharmacokinetics, (2004) 43/2 (97-120).
Refs: 81
ISSN: 0312-5963 CODEN: CPKNDH
COUNTRY: New Zealand
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 003 Endocrinology
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
039 Pharmacy
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The prevalence and medical and economic impact of type 2 diabetes mellitus is increasing in Western societies. New agents have been developed that act primarily to reduce postprandial glucose excursions, which may be of particular significance now that postprandial glucose excursions are known to be correlated with cardiovascular morbidity and mortality. Nateglinide is a phenylalanine derivative that blocks K(+) channels in pancreatic β-cells, facilitating insulin secretion. Nateglinide sensitises β-cells to ambient glucose, reducing the glucose concentration needed to stimulate insulin secretion. The pharmacokinetics of nateglinide are characterised by rapid absorption and elimination, with good (73%) bioavailability. Nateglinide is more rapidly absorbed when given 0-30 minutes prior to meal ingestion than if given during the meal. Nateglinide is extensively metabolised, primarily by cytochrome P450 2C9, and eliminated primarily by the kidney. Nateglinide pharmacokinetics are linear over the dose range 60-240mg. No significant pharmacokinetic alterations occur in renally impaired patients, in the elderly, or in mildly hepatically impaired patients. Nateglinide administered prior to meals stimulates rapid, short-lived insulin secretion in a dose-dependent manner, thus decreasing mealtime plasma glucose excursions. Its effects on insulin secretion are synergistic with those of a meal. With increasing nateglinide doses, the risk of hypoglycaemia also increases, but its incidence is low. Even if a meal is missed, and the patient skips the dose of nateglinide (as recommended in the event of a missed meal), the incidence of subsequent hypoglycaemia remains low compared with long-acting agents. The postprandial insulinotropic effects of nateglinide are more rapid than those of repaglinide and more rapid and greater than those of glibenclamide (glyburide), while producing less prolonged insulin exposure and less risk of delayed hypoglycaemia. Further investigation is required to determine if nateglinide inhibition of postprandial glucose excursions will help to prevent diabetic complications or preserve pancreatic β-cell function.

L4 ANSWER 19 OF 24 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2003422728 EMBASE
TITLE: [Current oral agents for type 2 diabetes]. TIP 2 DIYABETTE GUNCEL ORAL AJANLAR.
AUTHOR: Stoller W.A.
SOURCE: SENDROM, (2003) 15/6 (24-33).
Refs: 22
ISSN: 1016-5134 CODEN: SENDEY

COUNTRY: Turkey
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 003 Endocrinology
017 Public Health, Social Medicine and Epidemiology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: Turkish
SUMMARY LANGUAGE: English; Turkish
AB Type 2 diabetes has reached epidemic levels in the United States. Progressive evidence has emphasized the importance of glucose control in avoiding the high costs and reduced quality of life associated with the numerous complications of diabetes. Fortunately, pharmacologic options for treating type 2 diabetes have increased dramatically during the last 6 years, allowing new opportunities for successful outcomes. Such options will continue to expand. Therefore we are challenged to effectively use these agents in a logical progressive regimen while minimizing side effects.

L4 ANSWER 20 OF 24 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2003324437 EMBASE
TITLE: Sulphonylurea action revisited: The post-cloning era.
AUTHOR: Gribble F.M.; Reimann F.
CORPORATE SOURCE: Dr. F.M. Gribble, Department of Clinical Biochemistry, Addenbrooke's Hospital, Box 232, Hills Road, Cambridge, CB2 2QR, United Kingdom. fmg23@cam.ac.uk
SOURCE: Diabetologia, (1 Jul 2003) 46/7 (875-891).
Refs: 163
ISSN: 0012-186X CODEN: DBTGAJ
COUNTRY: Germany
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 003 Endocrinology
006 Internal Medicine
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Hypoglycaemic agents such as sulphonylureas and the newer group of "glinides" stimulate insulin secretion by closing ATP-sensitive potassium (K(ATP)) channels in pancreatic beta cells, but have varying cross-reactivity with related channels in extrapancreatic tissues such as heart, vascular smooth and skeletal muscle. Experiments on the structure-function relationships of recombinant K(ATP) channels and the phenotypes of mice deficient in different K(ATP) channel subunits have provided important insights into the mechanisms underlying sulphonylurea selectivity, and the potential consequences of K(ATP) channel blockade outside the pancreatic beta cell. The different pharmacological properties of K(ATP) channels from beta cells compared with those from cardiac, smooth and skeletal muscle, are accounted for by the expression of alternative types of sulphonylurea receptor, with non-identical drug binding sites. The sulphonylureas and glinides are found to fall into two groups: one exhibiting selectivity for beta cell sulphonylurea receptors (SUR1), and the other blocking cardiovascular and skeletal muscle sulphonylurea receptors (SUR2) with potencies similar to their action on SUR1. In seeking potential side effects of K(ATP) channel inhibitors in humans, it is essential to take these drug differences into account, along with the probability (suggested by the studies on K(ATP) channel knockout mice) that the effects of extrapancreatic K(ATP) channel inhibition might be either subtle or rare. Further studies are still required before a final decision can be made on whether non-selective agents are appropriate for the therapy of Type 2 diabetes.

L4 ANSWER 21 OF 24 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.

on STN
ACCESSION NUMBER: 2002306128 EMBASE
TITLE: Study of the insulinotropic effect of the novel antihyperglycemic agent KAD-1229 using HIT T15 cells, a hamster's insulinoma cell line.
AUTHOR: Ichikawa K.; Yamato T.; Tsuji A.; Ojima K.; Kusama H.; Kojima M.
CORPORATE SOURCE: Dr. K. Ichikawa, Pharmacology Laboratories, Kissei Pharmaceutical Co., Ltd., 4365-1, Kashiwabara, Minamiazumi, Nagano 399-8304, Japan. kiyoshi_ichikawa@pharm.kissei.co.jp
SOURCE: Arzneimittel-Forschung/Drug Research, (2002) 52/8 (605-609).
Refs: 10
ISSN: 0004-4172 CODEN: ARZNAD
COUNTRY: Germany
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 003 Endocrinology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English; German
AB The insulinotropic effect of (+)-monocalcium bis [(2S)-2-benzyl-3-(cis-hexahydro-2-isoindolinyl-carbonyl) propionate] dihydrate (CAS 145375-43-5, KAD-1229) was assessed by comparing it with those of glibenclamide (CAS 10238-21-8), nategliulde (CAS 105016-04-4), and repaglinide (CAS 135062-02-1) using HIT T15 cells, a hamster insulinoma cell line. Although their potencies were different, KAD-1229, glibenclamide, nateglinide, and repaglinide all concentration-dependently and significantly induced insulin release from these cells. Further, each agent displaced the binding of (3)H-glibenclamide to the cell membrane and inhibited (86)Rb(+) efflux from the cells. These results indicate that KAD-1229, glibenclamide, nateglinide, and repaglinide each exert their insulinotropic effect by binding to the glibenclamide binding sites (sulfonylurea receptors) on pancreatic β-cells and closing K(+) channels. Diazoxide, a K(+) channel opener, and ultrendipine, a Ca(2+) blocker, suppressed the insulin release induced by KAD-1229 or glibenclamide. These results demonstrate that the insulinotropic actions of KAD-1229 and ghbenclamide involve similar underlying pathways.

L4 ANSWER 22 OF 24 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2000178950 EMBASE
TITLE: CFTR and disease: Implications for drug development.
AUTHOR: Super M.
CORPORATE SOURCE: M. Super, Regional Cystic Fibrosis Centre, Royal Manchester Children's Hospital, Manchester M27 4HA, United Kingdom
SOURCE: Lancet, (27 May 2000) 355/9218 (1840-1842).
Refs: 15
ISSN: 0140-6736 CODEN: LANCAO
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Note
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
015 Chest Diseases, Thoracic Surgery and Tuberculosis
029 Clinical Biochemistry
037 Drug Literature Index
LANGUAGE: English

L4 ANSWER 23 OF 24 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2000:515057 BIOSIS
DOCUMENT NUMBER: PREV200000515057
TITLE: Uptake of radioactive molecules by the exocrine and endocrine pancreas in the perspective of non-invasive imaging.
AUTHOR(S): Malaisse, Willy J. [Reprint author]

CORPORATE SOURCE: Laboratory of Experimental Medicine, Brussels Free University, 808 Route de Lennik, B-1070, Brussels, Belgium
SOURCE: International Journal of Molecular Medicine, (2000) Vol. 6, No. Supplement 1, pp. S7. print.
Meeting Info.: Joint Meeting of the 5th World Congress on Advances in Oncology and the 3rd International Symposium on Molecular Medicine. Crete, Greece. October 19-21, 2000.
ISSN: 1107-3756.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 29 Nov 2000
Last Updated on STN: 11 Jan 2002

L4 ANSWER 24 OF 24 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2001125804 EMBASE
TITLE: Purdue diabetic licence cancelled.
SOURCE: Manufacturing Chemist, (2001) 72/3 (13).
ISSN: 0262-4230 CODEN: MCHMDI
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Note
FILE SEGMENT: 037 Drug Literature Index
039 Pharmacy
LANGUAGE: English

=> d his

(FILE 'HOME' ENTERED AT 15:27:19 ON 19 MAY 2004)

FILE 'MEDLINE, BIOSIS, EMBASE' ENTERED AT 15:27:34 ON 19 MAY 2004
L1 36 S MITIGLINIDE
L2 0 S L1 AND (INFLAMMATORY OR INFLAMMATION OR NEUROPATHY OR NEUROPA
L3 24 DUP REM L1 (12 DUPLICATES REMOVED)
L4 24 FOCUS L3 1-

=> s l1 or kad 1229 or s 21403
L5 134 L1 OR KAD 1229 OR S 21403

=> s l5 and (inflammatory or inflammation or neuropathy or neuropathies or pain)
L6 1 L5 AND (INFLAMMATORY OR INFLAMMATION OR NEUROPATHY OR NEUROPATH IES OR PAIN)

=> d ibib abs it
'IT' IS NOT A VALID FORMAT FOR FILE 'EMBASE'

The following are valid formats:

The default display format is BIB.

ABS --------- AB
ALL --------- AN, DN, TI, AU, CS, SO, PUI, CY, DT, FS, LA, SL, AB, CT, RN, CN, NP, CO, GEN
BIB --------- AN, DN, TI, AU, CS, SO, PUI, CY, DT, FS, LA, SL
CBIB -------- Compressed bibliographic data
DALL -------- ALL, delimited for post-processing
IABS -------- ABS, with a text label
IALL -------- ALL, indented with text labels
IBIB -------- BIB, indented with text labels
IND --------- CT, RN, CN, NP, CO, GEN
TRIAL ------ TI, CT, RN, CN, NP, CO, GEN (SAM, TRI)
HIT --------- All fields containing hit terms

HITIND ------ IND
KWIC -------- All hit terms plus 20 words on either side
OCC --------- List of display fields containing hit terms
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ENTER DISPLAY FORMAT (BIB):end

=> d ibib abs

L6 ANSWER 1 OF 1 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN
ACCESSION NUMBER: 1998369739 EMBASE
TITLE: Novel therapeutic strategies for the treatment of Type 2 diabetes.
AUTHOR: Perfetti R.; Barnett P.S.; Mathur R.; Egan J.M.
CORPORATE SOURCE: Dr. R. Perfetti, Division of Endocrinology Metabolism, Department of Medicine, Cedars-Sinai Medical Center, 8700 Beverly Blvd., Los Angeles, CA 90048, United States
SOURCE: Diabetes/Metabolism Reviews, (1998) 14/3 (207-225).
Refs: 126
ISSN: 0742-4221 CODEN: DMREEG
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 003 Endocrinology
006 Internal Medicine
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Diabetes mellitus is the most common endocrine disease, accounting for over 200 million people affected worldwide. It is characterized by a lack of insulin secretion and/or increased cellular resistance to insulin, resulting in hyperglycemia and other metabolic disturbances. People with diabetes suffer from increased morbidity and premature mortality related to cardiovascular, microvascular and neuropathic complications. The Diabetes Control and Complication Trial (DCCT) has convincingly demonstrated the relationship of hyperglycemia to the development and progression of complications and showed that improved glycemic control reduced these complications. Although the DCCT exclusively studied patients with Type 1 diabetes, there is ample evidence to support the belief that the same relationship between metabolic control and clinical outcome exists in patients with Type 2 diabetes. Therefore, a major effort should be made to develop and implement more effective treatment regimes. This article reviews those novel drugs that have been recently introduced for the management of Type 2 diabetes, or that have reached an advanced level of study and will soon be proposed for preliminary clinical trials. They include: (i) compounds that promote the synthesis/secretion of insulin by the β-cell; (ii) inhibitors of the α-glucosidase activity of the small intestine; (iii) substances that enhance the action of insulin at the level of the target tissues; and (iv) inhibitors of free fatty acid oxidation.

=> s l5 and complication
L7 11 L5 AND COMPLICATION

=> focus
PROCESSING COMPLETED FOR L7
L8 11 FOCUS L7 1-

=> d ibib abs 1-11

L8 ANSWER 1 OF 11 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1996:474940 BIOSIS
DOCUMENT NUMBER: PREV199699204496
TITLE: A rapid and short-acting hypoglycemic agent **KAD-1229** improves post-prandial hyperglycemia and diabetic **complications** in streptozotocin-induced non-insulin-dependent diabetes mellitus rats.
AUTHOR(S): Ohnota, Hideki [Reprint author]; Kitamura, Tsuyoshi; Kinukawa, Mayumi [Reprint author]; Hamano, Shuichiro [Reprint author]; Shibata, Nobuo; Miyata, Hiroshi [Reprint author]; Ujiie, Arao [Reprint author]
CORPORATE SOURCE: Central Res. Lab., Kissei Pharmaceutical Co. Ltd., 4365-1 Kashiwabara, Hotaka, Minamiazumi-gun, Nagano 399-83, Japan
SOURCE: Japanese Journal of Pharmacology, (1996) Vol. 71, No. 4, pp. 315-323.
CODEN: JJPAAZ. ISSN: 0021-5198.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 24 Oct 1996
Last Updated on STN: 24 Oct 1996
AB We investigated therapeutic effects of a rapid- and short-acting non-sulfonylurea hypoglycemic agent, calcium (2S)-2-benzyl-3-(cis-hexahydro-2-isoindolinylcarbonyl)propionate dihydrate (**KAD-1229**), on streptozotocin (STZ)-induced non-insulin-dependent diabetes mellitus (NIDDM) rats. The effects exerted by **KAD-1229** on the post-prandial plasma glucose rise in STZ-induced mild NIDDM (mNIDDM) rats were different from those of sulfonylureas. When **KAD-1229** with liquid meal (10 kcal/kg) was given to the mNIDDM rats, the plasma glucose migration was similar to that of normal healthy rats. On the contrary, glibenclamide had little or no effect on the plasma glucose rise 0.5-1 hr after oral administration, and its effect was only evident 2-5 hr after dosing. Tolbutamide showed similar hypoglycemia to that induced by glibenclamide at 2-5 hr with insufficient efficacy at 0.5 hr. Gliclazide sufficiently suppressed the level of post-prandial plasma glucose. However, its complete inhibition of post-prandial plasma glucose was associated with the extra-hypoglycemia 1-5 hr after oral administration. We also tested the efficacy of **KAD-1229** in more severe STZ-induced NIDDM (sNIDDM) rats to elucidate the effects of the drug on the long-term glycemic controls and diabetic **complications**. When the sNIDDM rats were treated with 10 mg/kg **KAD-1229** twice a day for about 17 weeks, increases in fasting plasma glucose and hemoglobin A-1c were inhibited. Furthermore, treatment with **KAD-1229** suppressed the development of microalbuminuria and cortical cataract. We conclude that the rapid- and short-acting insulinotropic agent **KAD-1229** is able to improve the deterioration in the glycemic controls and inhibit the development of diabetic **complications** in STZ-induced NIDDM rats.

L8 ANSWER 2 OF 11 MEDLINE on STN
ACCESSION NUMBER: 97041658 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8886929
TITLE: A rapid- and short-acting hypoglycemic agent **KAD-1229** improves post-prandial hyperglycemia and

diabetic **complications** in streptozotocin-induced non-insulin-dependent diabetes mellitus rats.

AUTHOR: Ohnota H; Kitamura T; Kinukawa M; Hamano S; Shibata N; Miyata H; Ujiie A

CORPORATE SOURCE: Central Research Laboratories, Kissei Pharmaceutical Co., Ltd., Nagano, Japan.

SOURCE: Japanese journal of pharmacology, (1996 Aug) 71 (4) 315-23. Journal code: 2983305R. ISSN: 0021-5198.

PUB. COUNTRY: Japan

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199701

ENTRY DATE: Entered STN: 19970219
Last Updated on STN: 19970219
Entered Medline: 19970130

AB We investigated therapeutic effects of a rapid- and short-acting non-sulfonylurea hypoglycemic agent, calcium (2S)-2-benzyl-3-(cis-hexahydro-2-isoindolinylcarbonyl)propionate dihydrate (**KAD-1229**), on streptozotocin (STZ)-induced non-insulin-dependent diabetes mellitus (NIDDM) rats. The effects exerted by **KAD-1229** on the post-prandial plasma glucose rise in STZ-induced mild NIDDM (mNIDDM) rats were different from those of sulfonylureas. When **KAD-1229** with liquid meal (10 kcal/kg) was given to the mNIDDM rats, the plasma glucose migration was similar to that of normal healthy rats. On the contrary, glibenclamide had little or no effect on the plasma glucose rise 0.5-1 hr after oral administration, and its effect was only evident 2-5 hr after dosing. Tolbutamide showed similar hypoglycemia to that induced by glibenclamide at 2-5 hr with insufficient efficacy at 0.5 hr. Gliclazide sufficiently suppressed the level of post-prandial plasma glucose. However, its complete inhibition of post-prandial plasma glucose was associated with the extra-hypoglycemia 1-5 hr after oral administration. We also tested the efficacy of **KAD-1229** in more severe STZ-induced NIDDM (sNIDDM) rats to elucidate the effects of the drug on the long-term glycemic controls and diabetic **complications**. When the sNIDDM rats were treated with 10 mg/kg **KAD-1229** twice a day for about 17 weeks, increases in fasting plasma glucose and hemoglobin A1c were inhibited. Furthermore, treatment with **KAD-1229** suppressed the development of microalbuminuria and cortical cataract. We conclude that the rapid- and short-acting insulinotropic agent **KAD-1229** is able to improve the deterioration in the glycemic controls and inhibit the development of diabetic **complications** in STZ-induced NIDDM rats.

L8 ANSWER 3 OF 11 EMBASE on STN

ACCESSION NUMBER: 96286101 EMBASE

DOCUMENT NUMBER: 1996286101

TITLE: A rapid- and short-acting hypoglycemic agent **KAD-1229** improves post-prandial hyperglycemia and diabetic **complications** in streptozotocin-induced non-insulin-dependent diabetes mellitus rats.

AUTHOR: Ohnota H.; Kitamura T.; Kinukawa M.; Hamano S.; Shibata N.; Miyata H.; Ujiie A.

CORPORATE SOURCE: Central Research Laboratories, Kissei Pharmaceutical Co., Ltd., 4365-1 Kashiwabara,Hotaka, Nagano 399-83, Japan

SOURCE: Japanese Journal of Pharmacology, (1996) 71/4 (315-323). ISSN: 0021-5198 CODEN: JJPAAZ

COUNTRY: Japan

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 003 Endocrinology
030 Pharmacology
037 Drug Literature Index

LANGUAGE: English
SUMMARY LANGUAGE: English
AB We investigated therapeutic effects of a rapid- and short-acting non-sulfonylurea hypoglycemic agent, calcium (2S)-2-benzyl-3-(cis-hexahydro-2-isoindolinylcarbonyl)propionate dihydrate (**KAD-1229**), on streptozotocin (STZ)-induced non-insulin-dependent diabetes mellitus (NIDDM) rats. The effects exerted by **KAD-1229** on the post-prandial plasma glucose rise in STZ-induced mild NIDDM (mNIDDM) rats were different from those of sulfonylureas. When **KAD-1229** with liquid meal (10 kcal/kg) was given to the mNIDDM rats, the plasma glucose migration was similar to that of normal healthy rats. On the contrary, glibenclamide had little or no effect on the plasma glucose rise 0.5-1 hr after oral administration, and its effect was only evident 2-5 hr after dosing. Tolbutamide showed similar hypoglycemia to that induced by glibenclamide at 2-5 hr with insufficient efficacy at 0.5 hr. Gliclazide sufficiently suppressed the level of post-prandial plasma glucose. However, its complete inhibition of post-prandial plasma glucose was associated with the extra-hypoglycemia 1-5 hr after oral administration. We also tested the efficacy of **KAD-1229** in more severe STZ-induced NIDDM (sNIDDM) rats to elucidate the effects of the drug on the long-term glycemic controls and diabetic **complications**. When the sNIDDM rats were treated with 10 mg/kg **KAD-1229** twice a day for about 17 weeks, increases in fasting plasma glucose and hemoglobin A(1c) were inhibited. Furthermore, treatment with **KAD-1229** suppressed the development of microalbuminuria and cortical cataract. We conclude that the rapid- and short-acting insulinotropic agent **KAD-1229** is able to improve the deterioration in the glycemic controls and inhibit the development of diabetic **complications** in STZ-induced NIDDM rats.

L8 ANSWER 4 OF 11 EMBASE on STN
ACCESSION NUMBER: 1998369739 EMBASE
TITLE: Novel therapeutic strategies for the treatment of Type 2 diabetes.
AUTHOR: Perfetti R.; Barnett P.S.; Mathur R.; Egan J.M.
CORPORATE SOURCE: Dr. R. Perfetti, Division of Endocrinology Metabolism, Department of Medicine, Cedars-Sinai Medical Center, 8700 Beverly Blvd., Los Angeles, CA 90048, United States
SOURCE: Diabetes/Metabolism Reviews, (1998) 14/3 (207-225).
Refs: 126
ISSN: 0742-4221 CODEN: DMREEG
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 003 Endocrinology
006 Internal Medicine
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Diabetes mellitus is the most common endocrine disease, accounting for over 200 million people affected worldwide. It is characterized by a lack of insulin secretion and/or increased cellular resistance to insulin, resulting in hyperglycemia and other metabolic disturbances. People with diabetes suffer from increased morbidity and premature mortality related to cardiovascular, microvascular and neuropathic **complications**. The Diabetes Control and **Complication** Trial (DCCT) has convincingly demonstrated the relationship of hyperglycemia to the development and progression of **complications** and showed that improved glycemic control reduced these **complications**. Although the DCCT exclusively studied patients with Type 1 diabetes, there is ample evidence to support the belief that the same relationship between metabolic control and clinical outcome exists in patients with Type 2 diabetes. Therefore, a major effort should be made to develop and

implement more effective treatment regimes. This article reviews those novel drugs that have been recently introduced for the management of Type 2 diabetes, or that have reached an advanced level of study and will soon be proposed for preliminary clinical trials. They include: (i) compounds that promote the synthesis/secretion of insulin by the β-cell; (ii) inhibitors of the α-glucosidase activity of the small intestine; (iii) substances that enhance the action of insulin at the level of the target tissues; and (iv) inhibitors of free fatty acid oxidation.

L8 ANSWER 5 OF 11 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2004068924 EMBASE
TITLE: Novel strategies for the pharmacological management of type 2 diabetes.
AUTHOR: Nourparvar A.; Bulotta A.; Di Mario U.; Perfetti R.
CORPORATE SOURCE: R. Perfetti, Div. of Endocrinology and Metabolism, Cedars-Sinai Medical Center, SSB # 290, 8723 Alden Drive, Los Angeles, CA 90048, United States. perfettir@cshs.org
SOURCE: Trends in Pharmacological Sciences, (2004) 25/2 (86-91). Refs: 61
ISSN: 0165-6147 CODEN: TPHSDY
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 003 Endocrinology
030 Pharmacology
036 Health Policy, Economics and Management
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Type 2 diabetes is characterized by high concentrations of glucose in the blood, which is caused by decreased secretion of insulin from the pancreas and decreased insulin action. This condition is prevalent worldwide and is associated with morbidity and mortality secondary to **complications** such as myocardial infarction, stroke and end-stage renal disease. The importance of tight control of blood glucose in either preventing or delaying the progression of **complications** is recognized.
Currently, there are many therapeutic options to treat hyperglycemia in type 2 diabetes. However, tight control is difficult to achieve and is often associated with side-effects. Recent advances in understanding insulin secretion, action and signaling have led to the development of new pharmacological agents. In this article, we review new molecules that are promising candidates for the future management of diabetes, focusing on their mechanism of action, efficacy, safety profile and potential benefits compared with pharmacological agents that are available currently.

L8 ANSWER 6 OF 11 MEDLINE on STN

ACCESSION NUMBER: 2003345780 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12877090
TITLE: Nateglinide and **mitiglinide**.
AUTHOR: Odawara Masato
CORPORATE SOURCE: Department of Endocrinology and Metabolism, Toranomon Hospital.
SOURCE: Nippon rinsho. Japanese journal of clinical medicine, (2003 Jul) 61 (7) 1230-7. Ref: 12
Journal code: 0420546. ISSN: 0047-1852.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: Japanese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200309
ENTRY DATE: Entered STN: 20030725

Last Updated on STN: 20030926
Entered Medline: 20030925

AB Patients with type 2 diabetes mellitus are associated with insulin resistance and/or impaired insulin secretion. Previous observations indicate that Japanese patients with type 2 diabetes tend to have impaired insulin response after glycemic load more often than Caucasian counterparts. Recently it has been reported that hyperglycemia after glucose load is itself a risk factor for the development of cardiovascular **complications** in the absence of elevated fasting plasma glucose. Recent observations on the association of post-challenge or post-prandial hyperglycemia with cardiovascular events suggest that lowering post-prandial plasma glucose may protect patients from developing cardiovascular diseases. Results of STOP-NIDDM trial suggest that nateglinide, which attenuates post-prandial glycemic surge in type 2 diabetes, may also be helpful for the protection against cardiovascular events. Nateglinide exerts its effects shortly after its administration and the effects continue for only about 3 hours. The patients receiving this agent rarely gain weight and develop hypoglycemia. This agent exerts hypoglycemic effects additively with alpha-gulucosidase inhibitors or metformin.

L8 ANSWER 7 OF 11 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2000243994 EMBASE
TITLE: Potential new treatments for type 2 diabetes.
AUTHOR: Bailey C.J.
CORPORATE SOURCE: C.J. Bailey, Department Diabetes Research, School Life and Health Sciences, Aston University, Birmingham B4 7ET, United Kingdom. c.j.bailey@aston.ac.uk
SOURCE: Trends in Pharmacological Sciences, (2000) 21/7 (259-265). Refs: 75
ISSN: 0165-6147 CODEN: TPHSDY
PUBLISHER IDENT.: S 0165-6147(00)01506-6
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
005 General Pathology and Pathological Anatomy
006 Internal Medicine
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The heterogeneous pathogenesis and progressive natural history of type 2 diabetes mellitus (T2DM) contrive a formidable therapeutic challenge. Dual endocrine deficits of impaired insulin action (insulin resistance) and inadequate insulin secretion create an environment of chronic hyperglycaemia and general metabolic disarray. This inflicts a heavy burden of morbidity and premature mortality from cardiovascular diseases, microvascular disorders (e.g. retinopathy and nephropathy) and neuropathic conditions. Improving glycaemic control delays the onset and reduces the severity of these long-term **complications**. However, even with intensive use of current antidiabetic agents more than 50% of T2DM patients suffer poor glycaemic control and 18% develop serious **complications** within six years of diagnosis. Clearly, there is a need for new antidiabetic agents. Copyright (C) 2000 Elsevier Science Ltd.

L8 ANSWER 8 OF 11 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2000104644 EMBASE
TITLE: New agents for Type 2 diabetes.
AUTHOR: Nattrass M.; Bailey C.J.
CORPORATE SOURCE: M. Nattrass, Diabetes Resource Centre, Selly Oak Hospital, Birmingham, United Kingdom
SOURCE: Bailliere's Best Practice and Research in Clinical

Endocrinology and Metabolism, (1999) 13/2 (309-329).
Refs: 73
ISSN: 1521-690X CODEN: BBPMFY
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 003 Endocrinology
006 Internal Medicine
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Current agents for the treatment of Type 2 diabetes mellitus improve the metabolic profile but do not reinstate normality. They also reduce chronic diabetic **complications**, but they do not eliminate them. Thus, new agents with novel actions are required to complement and extend the capabilities of existing treatments. Insulin resistance and beta-cell failure, which are crucial components in the pathogenesis of Type 2 diabetes, remain the underlying targets for new drugs. Recently introduced agents include a short-acting non-sulphonylurea insulin-releaser, repaglinide, which synchronizes insulin secretion with meal digestion in order to reduce post-prandial hyperglycaemia. The thiazolidinedione drugs, troglitazone, rosiglitazone and pioglitazone represent a new class of agonists for the nuclear receptor peroxisome proliferator-activated receptor-gamma (PPARγ). PPARγ increases the transcription of certain insulin-sensitive genes, thereby improving insulin sensitivity. The intestinal lipase inhibitor orlistat and the satiety-inducer sibutramine are new weight-reducing agents that may benefit glycaemic control in obese Type 2 diabetes patients. Several further new insulin-releasing agents, and agents to retard carbohydrate digestion and modify lipid metabolism stand poised to enter the market. The extent to which they will benefit glycaemic control remains to be seen. However, the prospect of permanently arresting or reversing the progressive deterioration of Type 2 diabetes continues to evade therapeutic capture.

L8 ANSWER 9 OF 11 EMBASE
on STN
ACCESSION NUMBER: 2004105024 EMBASE
TITLE: Clinical Pharmacokinetics of Nateglinide: A Rapidly-Absorbed, Short-Acting Insulinotropic Agent.
AUTHOR: McLeod J.F.
CORPORATE SOURCE: Dr. J.F. McLeod, Novartis Pharmaceuticals, One Health Plaza, East Hanover, NJ 07936, United States. james.mcleod@pharma.novartis.com
SOURCE: Clinical Pharmacokinetics, (2004) 43/2 (97-120).
Refs: 81
ISSN: 0312-5963 CODEN: CPKNDH
COUNTRY: New Zealand
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 003 Endocrinology
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
039 Pharmacy
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The prevalence and medical and economic impact of type 2 diabetes mellitus is increasing in Western societies. New agents have been developed that act primarily to reduce postprandial glucose excursions, which may be of particular significance now that postprandial glucose excursions are known to be correlated with cardiovascular morbidity and mortality. Nateglinide is a phenylalanine derivative that blocks K(+) channels in pancreatic β-cells, facilitating insulin secretion. Nateglinide sensitises β-cells to ambient glucose, reducing the glucose concentration needed

to stimulate insulin secretion. The pharmacokinetics of nateglinide are characterised by rapid absorption and elimination, with good (73%) bioavailability. Nateglinide is more rapidly absorbed when given 0-30 minutes prior to meal ingestion than if given during the meal. Nateglinide is extensively metabolised, primarily by cytochrome P450 2C9, and eliminated primarily by the kidney. Nateglinide pharmacokinetics are linear over the dose range 60-240mg. No significant pharmacokinetic alterations occur in renally impaired patients, in the elderly, or in mildly hepatically impaired patients. Nateglinide administered prior to meals stimulates rapid, short-lived insulin secretion in a dose-dependent manner, thus decreasing mealtime plasma glucose excursions. Its effects on insulin secretion are synergistic with those of a meal. With increasing nateglinide doses, the risk of hypoglycaemia also increases, but its incidence is low. Even if a meal is missed, and the patient skips the dose of nateglinide (as recommended in the event of a missed meal), the incidence of subsequent hypoglycaemia remains low compared with long-acting agents. The postprandial insulinotropic effects of nateglinide are more rapid than those of repaglinide and more rapid and greater than those of glibenclamide (glyburide), while producing less prolonged insulin exposure and less risk of delayed hypoglycaemia. Further investigation is required to determine if nateglinide inhibition of postprandial glucose excursions will help to prevent diabetic **complications** or preserve pancreatic β-cell function.

L8 ANSWER 10 OF 11 EMBASE
on STN

ACCESSION NUMBER: 2003422728 EMBASE
TITLE: [Current oral agents for type 2 diabetes].
TIP 2 DIYABETTE GUNCEL ORAL AJANLAR.
AUTHOR: Stoller W.A.
SOURCE: SENDROM, (2003) 15/6 (24-33).
Refs: 22
ISSN: 1016-5134 CODEN: SENDEY
COUNTRY: Turkey
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 003 Endocrinology
017 Public Health, Social Medicine and Epidemiology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: Turkish
SUMMARY LANGUAGE: English; Turkish
AB Type 2 diabetes has reached epidemic levels in the United States. Progressive evidence has emphasized the importance of glucose control in avoiding the high costs and reduced quality of life associated with the numerous **complications** of diabetes. Fortunately, pharmacologic options for treating type 2 diabetes have increased dramatically during the last 6 years, allowing new opportunities for successful outcomes. Such options will continue to expand. Therefore we are challenged to effectively use these agents in a logical progressive regimen while minimizing side effects.

L8 ANSWER 11 OF 11 EMBASE
on STN

ACCESSION NUMBER: 1998381399 EMBASE
TITLE: New insulin secretagogues for the treatment of type 2 diabetes.
AUTHOR: Perfetti R.; Mathur R.; Egan J.M.
CORPORATE SOURCE: Dr. R. Perfetti, Div. of Endocrinology and Metabolism, Department of Medicine, Cedars-Sinai Medical Center, 8700 Beverly Blvd., Los Angeles, CA 90048, United States.
perfettir@csmc.edu
SOURCE: Disease Management and Clinical Outcomes, (1998) 1/4 (129-135).
Refs: 56

ISSN: 1088-3371 CODEN: DMCOF6
PUBLISHER IDENT.: S 1088-3371(98)00001-6
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 003 Endocrinology
006 Internal Medicine
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Diabetes mellitus is a complex disease that affects more than 16 million Americans. Type 2 diabetes is the most common of the hyperglycemia states and accounts for over 85% of diabetes worldwide. The prevalence of type 2 diabetes is closely linked to industrialization, affluence, and increased life expectancy and is estimated to be between 1 and 2% among Caucasians. In the United States, the prevalence of the disease is markedly increased among American Indians, African Americans, and Hispanics. The prevalence rate increases with age and degree of obesity. Increasing life expectancy on most of the planet suggests that the incidence of type 2 diabetes will significantly increase in the years to come. Although the pathogenesis of type 1 and type 2 diabetes is different, poor glycemic control inevitably results in increased morbidity and mortality of the affected population. Aggressive management of the disease from the time of onset is crucial to preventing and/or controlling long-term **complications**. In this paper, we review the state-of-the-art of novel insulin secretagogues, which are likely to be introduced into the clinical management of diabetes in the near future.

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Diabetic neuropathy

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Medline NLM **definition** of **Diabetic** Neuropathies: Peripheral, autonomic, and cranial nerve disorders that are associated with DIABETES MELLITUS. These conditions usually result from **diabetic** microvascular injury involving small blood vessels that supply nerves (VASA NERVORUM). Relatively common conditions which may be associated with **diabetic neuropathy** include third nerve palsy (see OCULOMOTOR NERVE DISEASES); MONONEUROPATHY; mononeuropathy multiplex; **diabetic** amyotrophy; a painful POLYNEUROPATHY; autonomic **neuropathy**; and thoracoabdominal **neuropathy**.

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MAIN SEARCH INDEX

Diabetic neuropathy

Definition

Diabetic neuropathy is a nerve disorder caused by diabetes mellitus. **Diabetic neuropathy** may be diffuse, affecting several parts of the body, or focal, affecting a specific nerve and part of the body.

Description

The nervous system consists of two major divisions: the central nervous systems (CNS) which includes the brain, the cranial nerves, and the spinal cord, and the peripheral nervous system (PNS) which includes the nerves that link the CNS with the sensory organs, muscles, blood vessels, and glands of the body. These peripheral nerves are either motor, meaning that they are involved in motor activity such as walking, or sensory, meaning that they carry sensory information back to the CNS. The PNS also works with the CNS to regulate involuntary (autonomic) processes such as breathing, heartbeat, blood pressure, etc.

There are two types of diffuse **diabetic neuropathy** that affect different nervous system functions. Diffuse peripheral **neuropathy** primarily affects

the limbs, damaging the nerves of the feet and hands. Autonomic **neuropathy** is the other form of diffuse **neuropathy** and it affects the heart and other internal organs.

Focal-or localized-**diabetic neuropathy** affects specific nerves, most commonly in the torso, leg, or head.

Diabetic neuropathy can lead to muscular weakness, loss of feeling or sensation, and loss of autonomic functions such as digestion, erection, bladder control, and sweating among others.

The longer a person has diabetes, the more likely the development of one or more forms of **neuropathy**. Approximately 60-70% of patients with diabetes have **neuropathy**, but only about 5% will experience painful symptoms.

Causes and symptoms

The exact cause of **diabetic neuropathy** is not known. Researchers believe that the process of nerve damage is related to high glucose concentrations in the blood that could cause chemical changes in nerves, disrupting their ability to effectively send messages. High blood glucose is also known to damage the blood vessels that carry oxygen and other nutrients to the nerves. In addition, some people may have a genetic predisposition to develop **neuropathy**.

There is a wide range of symptoms associated with **diabetic neuropathy**, and they depend on which nerves and parts of the body are affected and also on the type of **neuropathy** present. Some patients have very mild symptoms, while others are severely disabled.

Common symptoms of diffuse peripheral **neuropathy** include:

- numbness and feelings of tingling or burning
- insensitivity to pain
- needle-like jabs of pain
- extreme sensitivity to touch
- loss of balance and coordination

Common symptoms of diffuse autonomic **neuropathy** include:

- impaired urination and sexual function
- bladder infections
- stomach disorders, due to the impaired ability of the stomach to empty (gastric stasis)
- nausea, vomiting and bloating
- dizziness, lightheadedness, and fainting spells
- loss of appetite

Common symptoms of focal **neuropathy** include:

- pain in the front of a thigh
- severe pain in the lower back
- pain in the chest or stomach
- ache behind an eye
- double vision
- paralysis on one side of the face

In severe **diabetic neuropathy** loss of sensation can lead to injuries that are unnoticed, progressing to infections, ulceration and possibly amputation.

Diagnosis

The diagnosis of **neuropathy** is based on the symptoms that present during a physical exam. Pain assessment is usually the first step. Patients may have more than one type of pain, and the history helps the doctor determine whether a the pain has a neuropathic cause.

The exam may include:

- a screening test for lost sensation
- nerve conduction studies to check the flow of electric current through a nerve
- electromyography (EMG) to see how well muscles respond to electrical impulses transmitted by nearby nerves.
- ultrasound to show how the bladder and other parts of the urinary tract are functioning
- sometimes a nerve biopsy may be performed.

Specialists who treat **diabetic neuropathy** include:

- neurologists: specialists in nervous system disorders
- urologists: specialists in urinary tract disorder
- gastroenterologists: specialists in digestive disorders
- podiatrists: specialists in caring for the feet

Treatment

Treatment of **diabetic neuropathy** is usually focused on treating the symptoms associated with the **neuropathy** and addressing the underlying cause by improving the control of blood sugar levels, which may heal the early stages of **neuropathy**.

There is no cure for the permanent nerve damage caused by **neuropathy**. To help control pain, the choice of proven drug therapies has broadened during the past decade. Pain medication, such as the topical skin cream

capsaicin, is usually no stronger than codeine because of the potential for addiction with long-term use of such drugs. Four main classes of drugs are available for pain management, alone or in combination: tricyclic antidepressants (Imipramine, Nortriptyline), narcotic analgesics (Morphine), anticonvulsants (Carbamazepine, Gabapentin), and antiarrhythmics.

Prognosis

Early stage **diabetic neuropathy** can usually be reversed with good glucose control. Once nerve damage has occurred it cannot be reversed. The prognosis is largely dependent on the management of the underlying condition, diabetes, which may halt the progression of the **neuropathy** and improve symptoms. Recovery, if it occurs, is slow.

Prevention

Tight glucose control and the avoidance of alcohol and cigarettes help protect nerves from damage.

Terms:

Central nervous system (CNS)
Part of the nervous system consisting of the brain, cranial nerves, and spinal cord. The brain is the center of higher processes, such as thought and emotion, and is responsible for the coordination and control of bodily activities and the interpretation of information from the senses. The cranial nerves and spinal cord link the brain to the peripheral nervous system.

Diabetes mellitus
Disease characterized by the inability of the body to produce or respond properly to insulin, required by the body to convert glucose to energy.

Glucose
The type of sugar found in the blood.

Peripheral nervous system (PNS)
One of the two major divisions of the nervous system. PNS nerves link the central nervous system with sensory organs, muscles, blood vessels, and glands.

Resources:

Books

- Saudek, Christopher D., Richard R. Rubin, and Cynthia S. Shump. The Johns Hopkins Guide to Diabetes. Baltimore: The Johns Hopkins University Press, 1997.

Organizations

- American Diabetes Association. 1701 North Beauregard Street, Alexandria, VA 22311. (800) DIABETES (800-342-2383). http://www.diabetes.org/.
- Juvenile Diabetes Foundation. 120 Wall St., 19th Floor, New York, NY 10005. (800) 533-CURE. http://www.jdf.org/.

Author Information:

- Gary Gilles

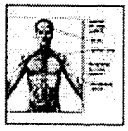
Diabetic Neuropathy

Alternate Names : Nerve Damage - **Diabetic**

Definition

A common complication of diabetes mellitus in which nerves are damaged as a result of hyperglycemia (high blood sugar levels).

Pictures & Images



Central Nervous System

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Overview, Causes, & Risk Factors

People with diabetes commonly develop temporary or permanent damage to nerve

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Herpes

Impotence

tissue. Nerve injuries are caused by decreased blood flow and high blood-sugar levels, and are more likely to develop if blood-glucose levels are poorly controlled. Some diabetics will not develop nerve damage, while others may develop this condition relatively early. On average, the onset of symptoms occurs 10 to 20 years after diabetes has been diagnosed. Approximately 50% of people with diabetes will eventually develop nerve damage.

Peripheral nerve injuries may affect cranial nerves or nerves from the spinal column and their branches. This type of **neuropathy** (nerve injury) tends to develop in stages. Early on, intermittent pain and tingling is noted in the extremities, particularly the feet. In later stages, the pain is more intense and constant. Finally, a painless **neuropathy** develops when pain sensation is lost to an area. This greatly increases the risk of severe tissue injury because pain no longer alerts the person to injury.

Autonomic neuropathies affect the nerves that regulate involuntary vital functions, including the heart muscle, smooth muscles and glands. Low blood pressure, diarrhea, constipation, sexual impotence, and other symptoms can be caused by autonomic neuropathies.

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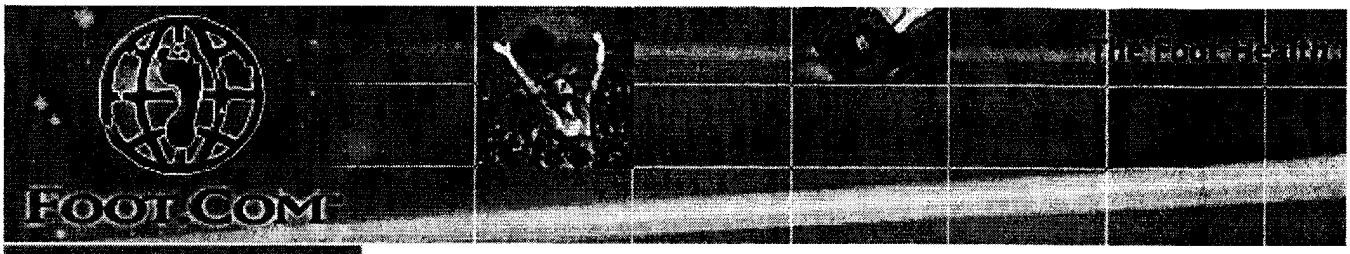
- Erection Problems
- Eyelid Drooping
- Facial Paralysis
- Muscle Cramps
- Numbness and Tingling
- Peripheral
- Physical Examination
- Speech Impairment (Adult)
- Swallowing Difficulty
- Urinary Incontinence
- Weakness

Review Date : 5/12/2002
Reviewed By : Stephanie Fish, M.D., Division of Endocrinology, University of Pennsylvania Medical Center, Philadelphia, PA. Review provided by VeriMed Healthcare Network.

Main Page of **Diabetic Neuropathy**



Conditions & Treatments
- Achilles Tendonitis
- AIDS & Your Feet
- Arch Pain / Arch Strain
- Arthritis
- Athlete's Foot
- Bunions (Bunionettes)
- Calluses
- Claw Toes
- Corns
- **Diabetic** Feet
- Hammer Toes
- Heel Fissures (Cracked Heels)
- Heel Pain
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- Ingrown Toenails
- Mallet Toes
- Metatarsalgia
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- **Neuropathy**
- Over Pronation (Flat Feet)
- Overlapping Toes
- Plantar Fasciitis
- Post-Tib Tendonitis
- Pregnancy & Your Feet
- Sesamoiditis
- Shin Splints
- Toenail Fungus

Pain Identifier
Foot Facts
The Sports Center
The Diabetes Center
FAQ

Foot Pain Identifier

Foot Pain Identifier
- Click where it hurts, find out what helps.

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Neuropathy

Definition

Of the 16 million Americans with diabetes, 25% develop foot problems related to the disease. This is primarily due to a condition called **neuropathy**. **Diabetic Neuropathy** is a complication of diabetes that affects the nerves. The most common type of **diabetic neuropathy** is called peripheral **neuropathy** and affects the peripheral nerves. Peripheral nerves are the nerves that go out from the brain and spinal cord to the muscles, skin, internal organs, and glands. Peripheral **neuropathy** impairs proper functioning of these sensory and motor nerves. The most common symptoms of **neuropathy** include numbness and loss of feeling, usually in the feet and hands.

Cause

Diabetic Neuropathy can cause insensitivity or a loss of ability to feel pain, heat, and cold. Diabetics suffering from **neuropathy** can develop minor cuts, scrapes, blisters, or pressure sores that they may not be aware of due to the insensitivity. If these minor injuries are left untreated, complications may result and lead to ulceration and possibly even amputation. **Neuropathy** can also cause deformities such as Bunions, Hammer Toes, and Charcot Feet.

It is very important for diabetics to take the necessary precautions to prevent all foot-related injuries. Due to the consequences of **neuropathy**, daily observation of the feet is critical. When a **diabetic** patient takes the necessary preventative footcare measures, he or she reduces the risk of developing serious foot conditions.

Treatment and Prevention

The most successful way to prevent **diabetic neuropathy** from occurring is to control the diabetes. It is important to maintain blood sugars at normal levels and maintain normal blood pressure. In addition to this, it is important to:

- Stop Smoking
- Limit the amount of alcohol you drink
- Have regular physical exams
- Have regular blood and urine tests
- Exercise regularly, according to your doctor's recommendation.

It is important for diabetics to treat their feet properly to avoid any future problems. Footwear and foot orthotics play an important role in **diabetic** footcare. Footwear that fits poorly can cause irritation and injury. Orthotics designed with Plastazote®, the #1 material for protecting the insensitive **diabetic** foot, are also frequently recommended. Plastazote is a material designed to accommodate pressure "hot spots" by conforming to heat and pressure. By customizing to the foot, Plastazote provides the comfort and protection needed in **diabetic** footcare. Footwear constructed with Plastazote is often recommended for the **diabetic** patient.

- **Diabetic** footwear should also provide the following benefits:
- High, wide toe box (high and wide space in the toe area)
- Removable insoles for fitting flexibility and the option to insert orthotics if necessary
- Rocker soles, designed to reduce pressure in the areas of the foot most susceptible to pain, most notably the heel and the ball-of-the-foot.
- Firm Heel Counters for extra and support and stability.

It is important for diabetics with **neuropathy** to take the necessary precautions to prevent injury and keep their feet healthy. If you have diabetes and are experiencing a foot problem, immediately consult with your foot doctor.

DIABETIC NEUROPATHY - DIABETIC NERVE DAMAGE

What is it ?

After **diabetes** has been present for only a short time, chemical and other changes can occur in the nerves of your body. These changes can cause either temporary or more permanent nerve damage. Such damage interferes with the conduction of impulses through the nerves. There may be no symptoms of this whatsoever. Conversely, a symptom of nerve damage may be the very first sign that **diabetes** has developed. Double vision may occur from damage to the nerves controlling eye movements; or one side of the face may droop due to damage to the facial nerve.

Foot movements on one side may become weak (foot drop), or there may be generalised weakness of all muscles in the body with fatigue. This is called motor **neuropathy**. The changes often reverse quite quickly when **diabetes** is brought under control with **treatment**. Some of the most common symptoms affect feeling. After several years of **diabetes**, numbness and tingling may occur, particularly in the feet.

You may not be aware of cuts, blisters or infections, particularly if they are on the soles of the feet. Indeed, an inability to feel pain may be a reason for a unrecognised cut or injury becoming

infected. Some people with **neuropathy** develop gnawing, sharp or stabbing nerve pains, which can be most unpleasant. Even joints can become damaged, deformed and swollen if the nerves which supply them are damaged. It is the ankle which is particularly at risk. Charcot's **neuropathy** or neuro-arthropathy are terms used to describe this uncommon but serious complication. All these conditions are all referred to as different types of sensory **neuropathy**.

In addition, more subtle (but very important) damage can occur to so-called autonomic nerves. These nerves do not control movement or feeling, but regulate many of the body's functions of which we are mostly unaware - until something goes seriously wrong. The bladder may not empty properly causing a wide variety of urinary symptoms, including a poor stream and a need to pass urine either less often or more often than usual. In males, impotence may occur. Blood pressure control may be lost, with a fall of pressure on standing, which causes giddiness or fainting. Even the bowel may be affected, with episodes of constipation, diarrhoea or incontinence.

How does it occur ?

When levels of blood **glucose** run above normal, the **glucose** which leaks into nerve cells is converted to chemicals which damage the nerve fibres. These then do not function properly. Early changes may be reversible, if blood **glucose** levels are brought under control. However, after a period of time, the nerve becomes permanently damaged: little or no recovery of function is then possible. In addition to these chemical changes, the tiny blood vessels, which feed the nerves may become blocked. It is then a lack of oxygen, which causes the nerve damage.

Why does it occur ?

Some people with **diabetes** seem particularly prone to nerve damage: others seem more resistant. This may be due to inborn differences in the way that **glucose** is processed in nerve cells. It is not known why different nerves are affected in different people. Nerve damage is much more common if **diabetes** is not well controlled. In these people, it is often too late to reverse the damage in the nerves once symptoms have developed. However, your doctor will regularly check your ankle reflexes and your ability to feel touch, pain and vibration. If such changes are present, it may be still possible to halt the damage.

Treatment Involved

Some additional tests may be carried out. The speed of

conduction of signals through the motor and sensory nerves can be measured, and the completeness of bladder emptying can also be checked in a number of ways. Once **neuropathy** is diagnosed, the first step will be to improve control of your blood **glucose** levels. This will mean attention to diet and exercise, and a probable change in the medication insulin or tablets. Your doctor will probably want you to run blood **glucose** levels that are mostly or always below 10mmol/litre (180mg/100ml), and lower than this before meals. He or she will pay particular attention to the blood test called haemoglobin A1c (HbA1c) levels. This indicates your overall **level** of **glucose** control over the previous 10 weeks or so. You will probably be advised to aim for levels below 7%.

If your feet are affected, you will be advised about avoiding barefoot walking and ensuring well-fitting shoes, which do not cause pressure. Your foot care should ideally be carried out by a registered chiropodist (podiatrist), and you will advised against self-**treatment** of any foot conditions. Even standard toenail care could be hazardous, especially if your eyesight is not perfect. Any minor injury could become infected, with ulceration and even infection of the underlying bone (osteomyelitis). Regular inspection of your feet will help to reduce these risks, and X-rays will be checked repeatedly if any chronic foot infection is present.. No drug is yet available to block the abnormal chemical reactions, which result in damages to nerves. Good blood **glucose** control is at present the only way of limiting nerve damage. Unpleasant tingling and pain may be helped by using low doses of anti-depressant drugs. Anti-convulsants (as used in epilepsy) reduce the sensitivity of nerve endings, and are also helpful in some cases.

During Treatment

If your bladder has been affected, your doctor may suggest a technique called triple voiding - passing urine again on two further occasions, five minutes apart, after each visit to the toilet. Completely emptying the bladder in this way helps to reduce the risk of infection. Giddiness and fainting due to blood pressure falls can be helped by a variety of medications, which raise the blood pressure. Sometimes, compression stockings on the legs help. Impotence treatment is dealt with separately. Bowel problems are treated either with drugs to control bowel activity or by antibiotics. These control bacterial growth in the bowel, which contributes to the diarrhoea, if present. The aim of better blood **glucose** control may increase the risk of low blood **glucose** levels (hypoglycaemia). In-between snacks and keeping emergency **glucose** sweets to hand both help to reduce this risk. The side-effects of other drugs is dealt with elsewhere.

After Treatment

Ongoing good diabetic control, together with care of your feet are essential if you wish to avoid further problems.

If Left Untreated

You would be at risk of worsening nerve symptoms. Many research studies have shown that better blood **glucose** control can markedly reduce the risk of significant nerve damage and it consequences. This has been shown separately for both type 1 **diabetes** (DCCT study) and for type 2 **diabetes** (UKPDS). Once **neuropathy** is established, a failure to treat the early problems of the feet can result in devastating infection, even leading to amputation.

Effects on Family

There is little that anyone other than the person with **diabetes** can do to help. Your family may however be happy to remind you about the details of foot care (which can be easily forgotten), and the need for regular medical checks to screen for the earliest signs of nerve damage.

Related Links

Click on link below
DIABETES TYPE 1 - INSULIN DEPENDENT **DIABETES**
DIABETES TYPE 2 - NON INSULIN DEPENDENT **DIABETES**
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IMPOTENCE - MALE ERECTILE DYSFUNCTION
DIABETIC DIET
ANTIDEPRESSANTS
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Diabetic Neuropathy

Contents:

What Is Diabetic Neuropathy?

Diabetic neuropathy is a nerve disorder caused by diabetes. Symptoms of neuropathy include numbness and sometimes pain in the hands, feet, or legs. Nerve damage caused by diabetes can also lead to problems with internal organs such as the digestive tract, heart, and sexual organs causing indigestion, diarrhea or constipation, dizziness, bladder infections, and impotence. In some cases, neuropathy can flare up suddenly, causing weakness and weight loss. Depression may follow. While some treatments are available, a great deal of research is still needed to understand how diabetes affects the nerves and to find more effective treatments for this complication.

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DCCT: Can Diabetic Neuropathy Be Prevented?

A 10-year clinical study that involved 1,441 volunteers with insulin-dependent diabetes (IDDM) was recently completed by the National Institute of Diabetes and Digestive and Kidney Diseases. The study proved that keeping blood sugar levels as close to the normal range as possible slows the onset and progression of nerve disease caused by diabetes. The Diabetes Control and Complications Trial (DCCT) studied two groups of volunteers: those who followed a standard diabetes management routine and those who intensively managed their diabetes. Persons in the intensive management group took multiple injections of insulin daily or used an insulin pump and monitored their blood glucose at least four times a day to try to lower their blood glucose levels to the normal range. After 5 years, tests of neurological function showed that the risk of nerve damage was reduced by 60 percent in the intensively managed group. People in the standard treatment group, whose average blood glucose levels were higher, had higher rates of neuropathy. Although the DCCT included only patients with IDDM, researchers believe that people with noninsulin-dependent diabetes would also benefit from maintaining lower levels of blood glucose.

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How Common Is Diabetic Neuropathy?

People with diabetes can develop nerve problems at any time. Significant clinical neuropathy can develop within the first 10 years after diagnosis of diabetes and the risk of developing neuropathy increases the longer a person has diabetes. Some recent studies have reported that:

- 60 percent of patients with diabetes have some form of neuropathy, but in most cases (30 to 40 percent), there are no symptoms.
- 30 to 40 percent of patients with diabetes have symptoms suggesting neuropathy, compared with 10 percent of people without diabetes.

Diabetic neuropathy appears to be more common in smokers, people over 40 years of age, and those who have had problems controlling their blood glucose levels.

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What Causes Diabetic Neuropathy?

Scientists do not know what causes diabetic neuropathy, but several factors are likely to contribute to the disorder. High blood glucose, a condition associated with diabetes, causes chemical changes in nerves. These changes impair the nerves' ability to transmit signals. High blood glucose also damages blood vessels that carry oxygen and nutrients to the nerves. In addition, inherited factors probably unrelated to diabetes may make some people more susceptible to nerve disease than others.

How high blood glucose leads to nerve damage is a subject of intense research. The precise

mechanism is not known. Researchers have discovered that high glucose levels affect many metabolic pathways in the nerves, leading to an accumulation of a sugar called sorbitol and depletion of a substance called myoinositol. However, studies in humans have not shown convincingly that these changes are the mechanism that causes nerve damage.

More recently, researchers have focused on the effects of excessive glucose metabolism on the amount of nitric oxide in nerves. Nitric oxide dilates blood vessels. In a person with diabetes, low levels of nitric oxide may lead to constriction of blood vessels supplying the nerve, contributing to nerve damage. Another promising area of research centers on the effect of high glucose attaching to proteins, altering the structure and function of the proteins and affecting vascular function.

Scientists are studying how these changes occur, how they are connected, how they cause nerve damage, and how to prevent and treat damage.

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What Are the Symptoms of Diabetic Neuropathy?

The symptoms of diabetic neuropathy vary. Numbness and tingling in feet are often the first sign. Some people notice no symptoms, while others are severely disabled. Neuropathy may cause both pain and insensitivity to pain in the same person. Often, symptoms are slight at first, and since most nerve damage occurs over a period of years, mild cases may go unnoticed for a long time. In some people, mainly those afflicted by focal neuropathy, the onset of pain may be sudden and severe.

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What Are the Major Types of Neuropathy?

The symptoms of neuropathy also depend on which nerves and what part of the body is affected. Neuropathy may be diffuse, affecting many parts of the body, or focal, affecting a single, specific nerve and part of the body.

Diffuse Neuropathy

The two categories of diffuse neuropathy are peripheral neuropathy affecting the feet and hands and autonomic neuropathy affecting the internal organs.

Peripheral Neuropathy

The most common type of peripheral neuropathy damages the nerves of the limbs, especially the feet. Nerves on both sides of the body are affected. Common symptoms of this kind of neuropathy are:

- Numbness or insensitivity to pain or temperature

- Tingling, burning, or prickling
- Sharp pains or cramps
- Extreme sensitivity to touch, even light touch
- Loss of balance and coordination.

These symptoms are often worse at night.

The damage to nerves often results in loss of reflexes and muscle weakness. The foot often becomes wider and shorter, the gait changes, and foot ulcers appear as pressure is put on parts of the foot that are less protected. Because of the loss of sensation, injuries may go unnoticed and often become infected. If ulcers or foot injuries are not treated in time, the infection may involve the bone and require amputation. However, problems caused by minor injuries can usually be controlled if they are caught in time. Avoiding foot injury by wearing well-fitted shoes and examining the feet daily can help prevent amputations.

Autonomic Neuropathy
(also called visceral neuropathy)
Autonomic neuropathy is another form of diffuse neuropathy. It affects the nerves that serve the heart and internal organs and produces changes in many processes and systems.

Urination and sexual response
Autonomic neuropathy most often affects the organs that control urination and sexual function. Nerve damage can prevent the bladder from emptying completely, so bacteria grow more easily in the urinary tract (bladder and kidneys). When the nerves of the bladder are damaged, a person may have difficulty knowing when the bladder is full or controlling it, resulting in urinary incontinence.

The nerve damage and circulatory problems of diabetes can also lead to a gradual loss of sexual response in both men and women, although sex drive is unchanged. A man may be unable to have erections or may reach sexual climax without ejaculating normally.

Digestion
Autonomic neuropathy can affect digestion. Nerve damage can cause the stomach to empty too slowly, a disorder called gastric stasis. When the condition is severe (gastroparesis), a person can have persistent nausea and vomiting, bloating, and loss of appetite. Blood glucose levels tend to fluctuate greatly with this condition.

If nerves in the esophagus are involved, swallowing may be difficult. Nerve damage to the bowels can cause constipation or frequent diarrhea, especially at night. Problems with the digestive system often lead to weight loss.

Cardiovascular system
Autonomic neuropathy can affect the cardiovascular system, which controls the circulation of blood throughout the body. Damage to this system interferes with the nerve impulses from various parts of the body that signal the need for blood and regulate blood pressure and heart rate. As a result, blood pressure may drop sharply after sitting or standing, causing a person to feel dizzy or light-headed, or even to faint (orthostatic hypotension).

Neuropathy that affects the cardiovascular system may also affect the perception of pain from heart disease. People may not experience angina as a warning sign of heart disease or may

suffer painless heart attacks. It may also raise the risk of a heart attack during general anesthesia.

Hypoglycemia
Autonomic neuropathy can hinder the body's normal response to low blood sugar or hypoglycemia, which makes it difficult to recognize and treat an insulin reaction.

Sweating
Autonomic neuropathy can affect the nerves that control sweating. Sometimes, nerve damage interferes with the activity of the sweat glands, making it difficult for the body to regulate its temperature. Other times, the result can be profuse sweating at night or while eating (gustatory sweating).

Focal Neuropathy

(including multiplex neuropathy)

Occasionally, diabetic neuropathy appears suddenly and affects specific nerves, most often in the torso, leg, or head. Focal neuropathy may cause:

- Pain in the front of a thigh
- Severe pain in the lower back or pelvis
- Pain in the chest, stomach, or flank
- Chest or abdominal pain sometimes mistaken for angina, heart attack, or appendicitis
- Aching behind an eye
- Inability to focus the eye
- Double vision
- Paralysis on one side of the face (Bell's palsy)
- Problems with hearing.

This kind of neuropathy is unpredictable and occurs most often in older people who have mild diabetes. Although focal neuropathy can be painful, it tends to improve by itself after a period of weeks or months without causing long-term damage.

People with diabetes are also prone to developing compression neuropathies. The most common form of compression neuropathy is carpal tunnel syndrome. Asymptomatic carpal tunnel syndrome occurs in 20 to 30 percent of people with diabetes, and symptomatic carpal tunnel syndrome occurs in 6 to 11 percent. Numbness and tingling of the hand are the most common symptoms. Muscle weakness may also develop.

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Diabetic Neuropathy Can Affect Virtually Every Part of the Body

Diffuse (Peripheral) Neuropathy

- Legs

- Feet
- Arms
- Hands

Diffuse (Autonomic) Neuropathy

- Heart
- Digestive System
- Sexual organs
- Urinary tract
- Sweat glands

Focal Neuropathy

- Eyes
- Facial muscles
- Hearing
- Pelvis and lower back
- Thigh
- Abdomen

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How Do Doctors Diagnose Diabetic Neuropathy?

A doctor diagnoses neuropathy based on symptoms and a physical exam. During the exam, the doctor may check muscle strength, reflexes, and sensitivity to position, vibration, temperature, and light touch. Sometimes special tests are also used to help determine the cause of symptoms and to suggest treatment.

A simple ***screening test*** to check point sensation in the feet can be done in the doctor's office. The test uses a nylon filament mounted on a small wand. The filament delivers a standardized 10-gram force when touched to areas of the foot. Patients who cannot sense pressure from the filament have lost protective sensation and are at risk for developing neuropathic foot ulcers. Physicians may order the filament (with instructions for use) free from the Gillis W. Long Hansen's Disease Center, LEAP Program, 5445 Point Clair Road, Carville, Louisiana 70721; telephone (504) 642-4714.

Nerve conduction studies check the flow of electrical current through a nerve. With this test, an image of the nerve impulse is projected on a screen as it transmits an electrical signal. Impulses that seem slower or weaker than usual indicate possible damage to the nerve. This test allows the doctor to assess the condition of all the nerves in the arms and legs.

Electromyography (EMG) is used to see how well muscles respond to electrical impulses transmitted by nearby nerves. The electrical activity of the muscle is displayed on a screen. A response that is slower or weaker than usual suggests damage to the nerve or muscle. This test is often done at the same time as nerve conduction studies.

Ultrasound employs sound waves. The sound waves are too high to hear, but they produce an image showing how well the bladder and other parts of the urinary tract are functioning.

Nerve biopsy involves removing a sample of nerve tissue for examination. This test is most often used in research settings.

If your doctor suspects autonomic neuropathy, you may also be referred to a physician who specializes in digestive disorders (gastroenterologist) for additional tests.

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How Is Diabetic Neuropathy Usually Treated?

Treatment aims to relieve discomfort and prevent further tissue damage. The first step is to bring blood sugar under control by diet and oral drugs or insulin injections, if needed, and by careful monitoring of blood sugar levels. Although symptoms can sometimes worsen at first as blood sugar is brought under control, maintaining lower blood sugar levels helps reverse the pain or loss of sensation that neuropathy can cause. Good control of blood sugar may also help prevent or delay the onset of further problems.

Another important part of treatment involves special care of the feet, which are prone to problems.

A number of medications and other approaches are used to relieve the symptoms of diabetic neuropathy.

Relief of Pain

For, burning, tingling, or numbness, the doctor may suggest an analgesic such as aspirin or acetaminophen or anti-inflammatory drugs containing ibuprofen. Nonsteroidal anti-inflammatory drugs should be used with caution in people with renal disease. Antidepressant medications such as amitriptyline (sometimes used with fluphenazine) or nerve medications such as carbamazepine or phenytoin sodium may be helpful. Codeine is sometimes prescribed for short-term use to relieve severe pain. In addition, a topical cream, capsaicin, is now available to help relieve the pain of neuropathy.

The doctor may also prescribe a therapy known as transcutaneous electronic nerve stimulations (TENS). In this treatment, small amounts of electricity block pain signals as they pass through a patient's skin. Other treatments include hypnosis, relaxation training, biofeedback, and acupuncture. Some people find that walking regularly or using elastic stockings helps relieve leg pain. Warm (not hot) baths, massage, or an analgesic ointment such as Ben Gay may also help.

Gastrointestinal Problems

Indigestion, belching, nausea, or vomiting are symptoms of gastroparesis. For patients with mild symptoms of slow stomach emptying, doctors suggest eating small, frequent meals and

avoiding fats. Eating less fiber may also relieve symptoms. For patients with severe gastroparesis, the doctor may prescribe metoclopramide, which speeds digestion and helps relieve nausea. Other drugs that help regulate digestion or reduce stomach acid secretion may also be used or erythromycine may be prescribed. In each case, the potential benefits of these drugs need to be weighed against their side effects.

To relieve diarrhea or other bowel problems, antibiotics or clonidine HCl, a drug used to treat high blood pressure, are sometimes prescribed. The antibiotic tetracycline may be prescribed. A wheat-free diet may also bring relief since the gluten in flour sometimes causes diarrhea.

Neurological problems affecting the urinary tract can result in infections or incontinence. The doctor may prescribe an antibiotic to clear up an infection and suggest drinking more fluids to prevent further infections. If incontinence is a problem, patients may be advised to urinate at regular times (every 3 hours, for example) since they may not be able to tell when the bladder is full.

Dizziness, Weakness

Sitting or standing slowly may help prevent light-headedness, dizziness, or fainting, which are symptoms that may be associated with some forms of autonomic neuropathy. Raising the head of the bed and wearing elastic stockings may also help. Increased salt in the diet and treatment with salt-retaining hormones such as fludrocortisone are other possible approaches. In certain patients, drugs used to treat hypertension can instead raise blood pressure, although predicting which patients will have this paradoxical reaction is difficult.

Muscle weakness or loss of coordination caused by diabetic neuropathy can often be helped by physical therapy.

Urinary and Sexual Problems

Nerve and circulatory problems of diabetes can disrupt normal male sexual function, resulting in impotence. After ruling out a hormonal cause of impotence, the doctor can provide information about methods available to treat impotence caused by neuropathy. Short-term solutions involve using a mechanical vacuum device or injecting a drug called a vasodilator into the penis before sex. Both methods raise blood flow to the penis, making it easier to have and maintain an erection. Surgical procedures, in which an inflatable or semirigid device is implanted in the penis, offer a more permanent solution. For some people, counseling may help relieve the stress caused by neuropathy and thereby help restore sexual function.

In women who feel their sexual life is not satisfactory, the role of diabetic neuropathy is less clear. Illness, vaginal or urinary tract infections, and anxiety about pregnancy complicated by diabetes can interfere with a woman's ability to enjoy intimacy. Infections can be reduced by good blood glucose control. Counseling may also help a woman identify and cope with sexual concerns.

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Why Is Good Foot Care Important for People with Diabetic Neuropathy?

People with diabetes need to take special care of their feet. Neuropathy and blood vessel disease both increase the risk of foot ulcers. The nerves to the feet are the longest in the body, and are most often affected by neuropathy. Because of the loss of sensation caused by neuropathy, sores or injuries to the feet may not be noticed and may become ulcerated.

At least 15 percent of all people with diabetes eventually have a foot ulcer, and 6 out of every 1,000 people with diabetes have an amputation. However, doctors estimate that nearly three quarters of all amputations caused by neuropathy and poor circulation could be prevented with careful foot care.

To prevent foot problems from developing, people with diabetes should follow these rules for foot care:

- Check your feet and toes daily for any cuts, sores, bruises, bumps, or infections--using a mirror if necessary.
- Wash your feet daily, using warm (not hot) water and a mild soap. If you have neuropathy, you should test the water temperature with your wrist before putting your feet in the water. Doctors do not advise soaking your feet for long periods, since you may lose protective calluses. Dry your feet carefully with a soft towel, especially between the toes.
- Cover your feet (except for the skin between the toes) with petroleum jelly, a lotion containing lanolin, or cold cream before putting on shoes and socks. In people with diabetes, the feet tend to sweat less than normal. Using a moisturizer helps prevent dry, cracked skin.
- Wear thick, soft socks and avoid wearing slippery stockings, mended stockings, or stockings with seams.
- Wear shoes that fit your feet well and allow your toes to move. Break in new shoes gradually, wearing them for only an hour at a time at first. After years of neuropathy, as reflexes are lost, the feet are likely to become wider and flatter. If you have difficulty finding shoes that fit, ask your doctor to refer you to a specialist, called a pedorthist, who can provide you with corrective shoes or inserts.
- Examine your shoes before putting them on to make sure they have no tears, sharp edges, or objects in them that might injure your feet.
- Never go barefoot, especially on the beach, hot sand, or rocks.
- Cut your toenails straight across, but be careful not to leave any sharp corners that could cut the next toe.
- Use an emery board or pumice stone to file away dead skin, but do not remove calluses, which act as protective padding. Do not try to cut off any growths yourself, and avoid using harsh chemicals such as wart remover on your feet.
- Test the water temperature with your elbow before stepping in a bath.
- If your feet are cold at night wear socks. (Do not use heating pads or hot water bottles.)
- Avoid sitting with your legs crossed. Crossing your legs can reduce the flow of blood to the feet.
- Ask your doctor to check your feet at every visit, and call your doctor if you notice that a sore is not healing well.
- If you are not able to take care of your own feet, ask your doctor to recommend a podiatrist (specialist in the care and treatment of feet) who can help.

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Are There Any Experimental Treatments for Diabetic Neuropathy?

Several new drugs under study may eventually prevent or reverse diabetic neuropathy. However, extensive testing is required by the U.S. Food and Drug Administration to establish the safety and efficacy of drugs before they are approved for widespread use.

Researchers are exploring treatment with a compound called myoinositol. Early findings have shown that nerves in diabetic animals and humans have less than normal amounts of this substance. Myoinositol supplements increase the levels of this substance in tissues of diabetic animals, but research is still needed to show any concrete lasting benefits from this treatment.

Another area of research concerns the drug aminoguanidine. In animals, this drug blocks cross-linking of proteins that occurs more quickly than normal in tissues exposed to high levels of glucose. Early clinical tests are under way to determine the effects of aminoguanidine in humans.

One approach that appeared promising involved the use of aldose reductase inhibitors (ARIs). ARIs are a class of drugs that block the formation of the sugar alcohol sorbitol, which is thought to damage nerves. Scientists hoped these drugs would prevent and might even repair nerve damage. But so far, clinical trials have shown that these drugs have major side effects and, consequently, they are not available for clinical use.

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Some General Hints

- Ask your doctor to suggest an exercise routine that is right for you. Many people who exercise regularly find the pain of neuropathy less severe. Aside from helping you reach and maintain a healthy weight, exercise also improves the body's use of insulin, helps improve circulation, and strengthens muscles. Check with your doctor before starting exercise that can be hard on your feet, such as running or aerobics.
- If you smoke, try to stop because smoking makes circulatory problems worse and increases the risk of neuropathy and heart disease.
- Reduce the amount of alcohol you drink. Recent research has indicated that as few as four drinks per week can worsen neuropathy.
- Take special care of your feet.

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What Resources Are Available for People with Diabetic Neuropathy?

American Association of Diabetes Educators
100 West Monroe Street, 4th Floor
Chicago, IL 60603
(800) 338-3633 or (312) 424-2426

A professional organization that can help individuals locate a diabetes educator in their community.

American Diabetes Association National Service Center
1660 Duke Street
Alexandria, VA 22314
(800) 232-3472 or (703) 549-1500

A private, voluntary organization that fosters public awareness of diabetes and supports and promotes diabetes research and education. The association has printed information on many aspects of diabetes, and local affiliates sponsor community programs. Local affiliates can be found in the telephone directory or through the national office.

American Dietetic Association
216 West Jackson Boulevard
Chicago, IL 60606-6995
(800) 877-1600 or (312) 899-0040

A professional organization that can help individuals locate a registered dietitian in their community.

American Heart Association
7320 Greenville Avenue
Dallas, TX 75231
(800) 242-1793

A private, voluntary organization that distributes literature on heart disease and how to prevent it. Local affiliates can be found in the telephone directory.

Juvenile Diabetes Foundation International
381 Park Avenue South
Suite 507
New York, NY 10016-8013
(212) 689-2860 or (800) 223-1138

A private, voluntary organization that funds research on diabetes and promotes public awareness. Local chapters located across the country sponsor programs and fund-raising activities. Information about local groups is available in telephone directories or from the national office.

National Diabetes Information Clearinghouse
1 Information Way
Bethesda, MD 20892-3560
(301) 654-3327

A program of the National Institute of Diabetes and Digestive and Kidney Diseases, the Federal Government's lead agency for diabetes research. The clearinghouse distributes a variety of publications to the public and to health professionals.

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Additional Reading

For more information about diabetic neuropathy and diabetes research:

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National Diabetes Information Clearinghouse

1 Information Way
Bethesda, MD 20892-3560
E-mail: ndic@info.niddk.**nih**.gov

The National Diabetes Information Clearinghouse (NDIC) is a service of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). The NIDDK is part of the National Institutes of Health under the U.S. Public Health Service. Established in 1978, the clearinghouse provides information about diabetes to people with diabetes and their families, health care professionals, and the public. NDIC answers inquiries; develops, reviews, and distributes publications; and works closely with professional and patient organizations and government agencies to coordinate resources about diabetes.

Publications produced by the clearinghouse are reviewed carefully for scientific accuracy, content, and readability.

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July **1995**

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Inflammation

Inflammation is a response of a tissue to injury, often injury caused by invading parasites. It is characterized by

- increased blood flow to the tissue causing
- increased temperature,
- redness,
- swelling, and
- pain.

A bacterial infection initiates **inflammation** through several interconnecting mechanisms:

- The "nonself" surface of bacteria allows the **complement system** to be activated through the "alternative pathway".
- Specific surface molecules of the bacteria, called Pathogen-Associated Molecular Patterns (PAMPs), bind to Toll-like receptors (TLRs) on a variety of leukocytes.

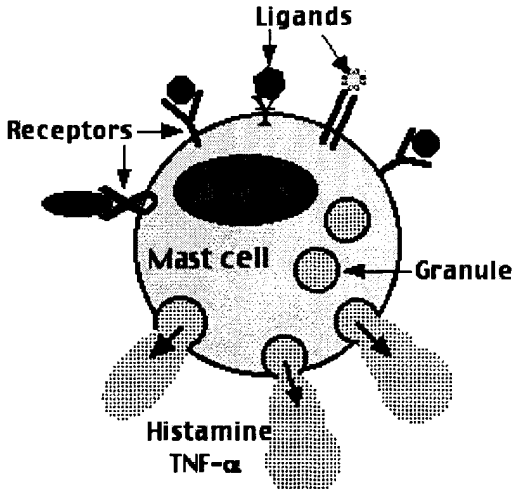
Link to discussion of PAMPs and TLRs.

Index to this page

Mast Cells

Mast cells are found in the tissues.

- Their cytoplasm is loaded with granules containing mediators of **inflammation**.
- Their surface is coated with a variety of receptors which, when engaged by the appropriate ligand, trigger exocytosis of the granules.



Mast cells appear to be key players in the initiation of **inflammation**.

- Their Toll-like receptors trigger exocytosis when they bind PAMPs like

  - the **lipopolysaccharide** (LPS or "endotoxin") of gram-negative bacteria (bind TLR-4)
  - the peptidoglycan of gram-positive bacteria (bind TLR-2)
- Their receptors for complement fragments trigger exocytosis when they bind
  - C3a and C5a
  - bacteria coated with C3b

Activated mast cells release literally dozens of potent mediators;

- some immediately as they discharge their granules
- some later as they synthesize them by new gene transcription

These mediators are active in either (or, in some cases, both)

- **recruiting** all the types of white blood cell to the site
  - monocytes that become macrophages when they leave the blood and enter the tissue
  - neutrophils
  - antigen-presenting dendritic cells
  - all kinds of lymphocytes:
    - B cells and T cells, leading to an adaptive immune response;
    - NK cells (an effector cell in innate immunity).
  - eosinophils
- **activating** many of these recruited cells to produce their own mediators of **inflammation**.

I shall not attempt to catalog all the players, but here are some of the major (and best understood) ones.

Tumor Necrosis Factor-alpha (TNF-α)

Large amounts of TNF-α are quickly released by stimulated mast cells. All the cells involved in **inflammation** have receptors for TNF-α, and are activated by it to synthesize more on their own. This positive feedback quickly amplifies the response.

Link to a description of how the binding of TNF-α to its receptors on a responding cell initiates new gene transcription by the cell.

Chemokines

These are **chemo**tactic cyto**kines**; that is, secreted proteins that attract other leukocytes into the area. Several have been identified.

Reactive Oxygen Species (ROS).

These are produced by activated phagocytes: macrophages and neutrophils. They are toxic for microorganisms but can also lead to tissue injury. ROS are described in detail on another page. Link to it.

Histamine.

The granules of mast cells are loaded with histamine and their exocytosis releases this potent mediator.

Histamine increases the blood flow to the area and the leakage of fluid and proteins from the blood into the tissue space. Thus the quick release of histamine is largely responsible for the redness and swelling associated with **inflammation**.

Interleukin-1 (IL-1).

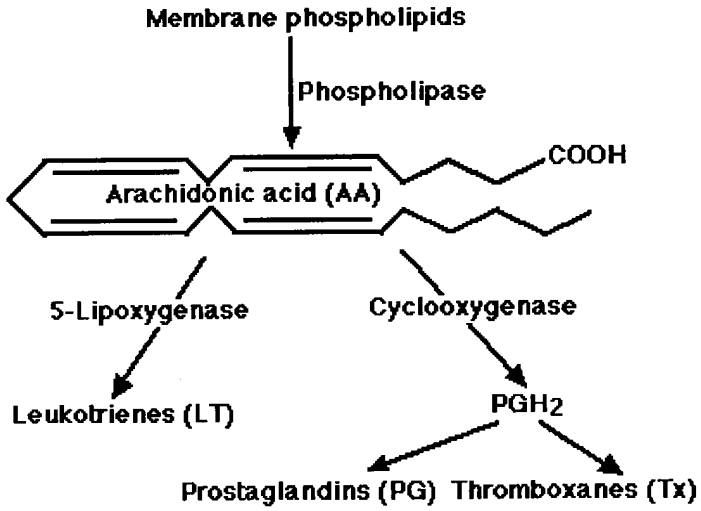
Macrophages and monocytes are the main source of this cytokine. IL-1 has both

- paracrine effects on cells in the vicinity, e.g.,
  - causing them to produce tissue factor and thus triggering the blood clotting cascade. [Link}
  - stimulating the synthesis and secretion of a variety of other interleukins
  - helping to activate T cells and thus initiate an adaptive immune response
- hormonal effects as it is carried in the blood throughout the body.
  - decreasing blood pressure
  - inducing fever.

IL-1 causes fever by stimulating the release of **prostaglandins**, which act on the temperature control center of the hypothalamus.

Leukotrienes and Prostaglandins

These potent mediators of **inflammation** are derivatives of **arachidonic acid** (**AA**) a 20-carbon unsaturated fatty acid produced from membrane phospholipids.



The principal pathways of arachidonic acid metabolism are

- the **5-lipoxygenase** pathway, which produces a collection of **leukotrienes** (**LT**) and
- the **cyclooxygenase** pathway, which produces prostaglandin H_2 (**PGH_2**). PGH_2 serves as the substrate for two enzymatic pathways: one leading to the production of several
  - **prostaglandins** (**PG**); the other leading to the production of
  - **thromboxanes** (**Tx**).

The Good Side of Inflammation

The inflammatory response to tissue damage is of great value. By

- isolating the damaged area,
- mobilizing effector cells and molecules to the site, and — in the late stages —
- promoting healing,

inflammation protects the body.

Its importance is demonstrated by the problems people with inherited defects in components of the process have with infections.

Some examples:

- a failure to produce reactive oxygen species (ROS) leads to **chronic granulomatous disease (CGD)** [Link to discussion]
- inherited defects in the ability to produce the later complement components (C5, C6, C7, C8, C9) increase the risk of certain infections.

The Bad Side of Inflammation

Often the inflammatory response is out of proportion to the threat it is dealing with. The result can be more damage to the body than the agent itself would have produced.

Allergies and Autoimmune Diseases

- All the many types of allergies and
- many of the autoimmune diseases

are examples of **inflammation** in response to what should have been a harmless, or at least noninfectious, agent.

Some examples:

- Asthma
- Rheumatoid Arthritis (RA)
- Multiple Sclerosis (MS)
- Systemic Lupus Erythematosus (SLE)
- Chronic Obstructive Pulmonary Disease (COPD)

In many of these cases, the problem is made worse by the formation of antibodies against

- self antigens or
- persistent antigens from smoldering infections.

The antibodies complex with the antigens triggering the **complement system** with all its mediators of **inflammation**.

The result: **immune complex disorders**.

Link to a discussion of several immune complex diseases.

Treating Inflammation

Inappropriate **inflammation** can be treated with

- **steroids** like the glucocorticoid **cortisol**

- **n**onsteroidal **a**nti-**i**nflammatory **d**rugs (NSAIDs) like aspirin and ibuprofen (e.g., Motrin®, Advil®).
- a number of proteins produced by recombinant DNA technology.

NonSteroidal Anti-Inflammatory Drugs (NSAIDs)

The NSAIDs achieve their effects by blocking the activity of cyclooxygenase.

In addition to reducing the fever and pain of **inflammation**, NSAIDs also inhibit clotting. They do this by interfering with the synthesis of thromboxane A_2 in platelets. This is the reason that

- aspirin is given to patients undergoing angioplasty;
- many men take a baby aspirin a day in the hope of avoiding heart attacks.

But regular use of NSAIDs has a downside: a tendency to develop ulcers in the stomach and duodenum.

Enter the COX-2 inhibitors.

COX-1 and COX-2

The body produces several different forms of cyclooxygenase (COX), including

- COX-1, which is involved in pain, clotting, and protecting the stomach;
- COX-2, which is involved in the pain produced by **inflammation**.

Most of the NSAIDs inhibit them both. However, some newer drugs, the so-called **COX-2 inhibitors**, such as

- rofecoxib (Vioxx®)
- celecoxib (Celebrex®)

are much more active against COX-2 than COX-1.

COX-2 inhibitors are effective against **inflammation** and seem to avoid damage to the GI tract. But, unfortunately, they increase the risk of heart attack because they do not block the synthesis of thromboxane A_2 by platelets (which contain only COX-1). So people depending on NSAIDs for their heart protective effects must monitor any use of COX-2 inhibitors carefully.

Therapeutic Proteins

Recombinant DNA and monoclonal antibody technology have produced some new therapies that are being enlisted in the battle against damaging **inflammation**.

- an IL-1 antagonist that binds and inactivates the IL-1 **receptor**.
- etanercept (Embrel®). A soluble version of the TNF-α **receptor**. It binds TNF-α preventing it from carrying out its many inflammatory actions. Potent but carries a severe risk of allowing infections to develop.
- **recombinant protein C**. To help the body dissolve the tiny clots that are triggered during **inflammation**.

- **infliximab** (Remicade®). A monoclonal antibody that binds to TNF-α. Shows promise against some inflammatory diseases such as rheumatoid arthritis. (Side-effect: can convert a latent case of tuberculosis into active disease.)

In fact, all the more powerful anti-inflammatory agents (e.g., glucocorticoids) increase the risk of infection.

Acute Inflammation: Sepsis and Septic Shock

On occasions, for reasons that are not entirely clear, the inflammatory response — usually to an infection by lipopolysaccharide (LPS)-bearing gram-negative bacteria — spirals out of control progressing until it involves the entire body. This life-threatening development is called **sepsis**.

One result is a breakdown in the control of blood clotting. What should have been a mechanism to help wall off an infected area and promote healing leads instead to a dangerous deposition of fibrin in small blood vessels throughout the body. This can lead to **septic shock**

- a failure of many organs: lungs, kidneys, etc.
- a sharp drop in blood pressure and, all too often,
- death

Toxic Shock Syndrome

Some gram-positive cocci can produce a similar condition, but here the eliciting agent is not LPS but a toxin liberated by the bacteria.

In theory, anti-inflammatory agents should be useful in combating sepsis. But so far, only recombinant protein C has shown any promise (by inhibiting the formation of thrombin), and severe bleeding is a dangerous side-effect.

Inflammation and Cancer

Chronic **inflammation** is also a frequent cause of cancer.

Read more in Bruce Ames's The Causes and Prevention of Cancer

- Liver cancer is often the sequel to years of **inflammation** caused by infection by hepatitis B and/or C viruses.
- Lung cancer often is the end stage of years of chronic **inflammation** caused by inhaled irritants, of which tobacco smoke is the most reliable.
- Cervical cancer can follow chronic infection and **inflammation** caused by
  - papilloma viruses
  - chlamydiae
- Bladder, colon, pancreas, stomach, and other **cancers** may similarly be the final stage of years of **inflammation**.

The strong link between chronic **inflammation** and cancer should not be surprising when you consider that

- the **reactive oxygen species** (ROS) liberated during **inflammation** are powerful DNA-damaging agents [Link];
- increased mitosis in response to **inflammation** puts more cells at risk of mutations as they replicate their DNA during S phase;
- Apoptosis, the programmed death of damaged cells, is suppressed in inflamed tissue. So cells with precancerous genetic mutations, which should have committed suicide, live on grow into a full-blown cancer.

Two Related Links:

- Allergies and **inflammation**
- Pain

Welcome&Next Search

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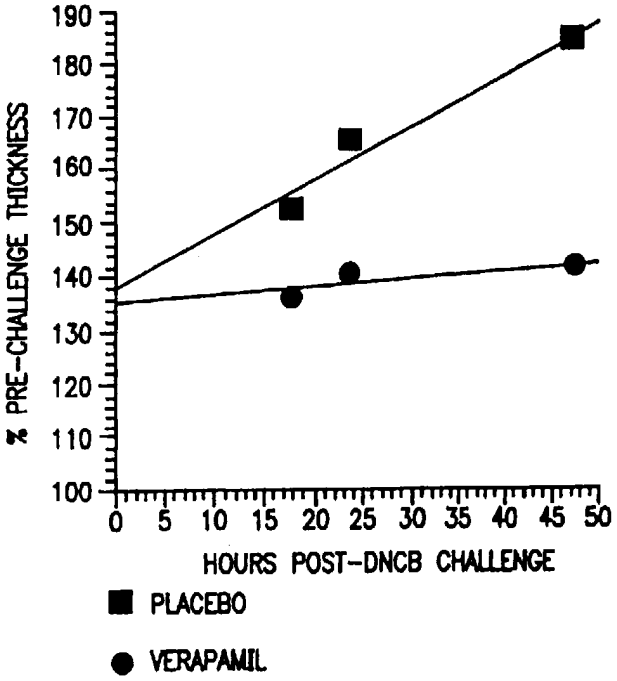

% PRE-CHALLENGE THICKNESS
190
180
170
160
150
140
130
120
110
100
0 5 10 15 20 25 30 35 40 45 50
HOURS POST-DNCB CHALLENGE
PLACEBO
VERAPAMIL

FIG. 3

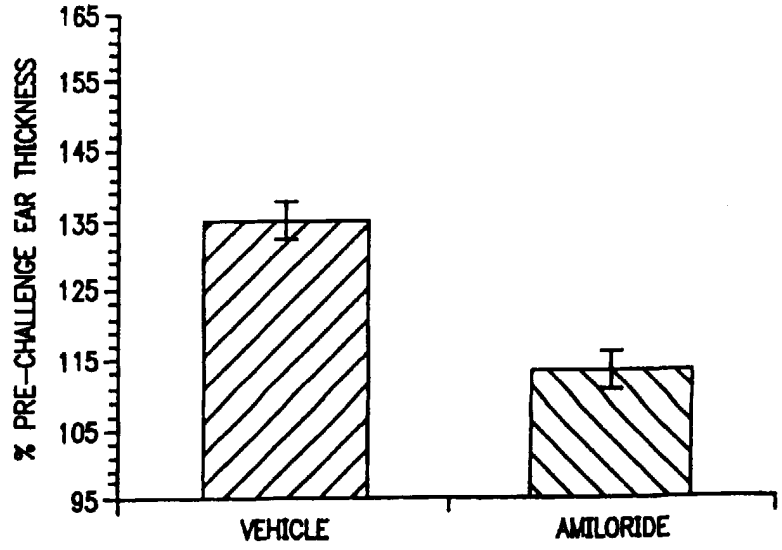
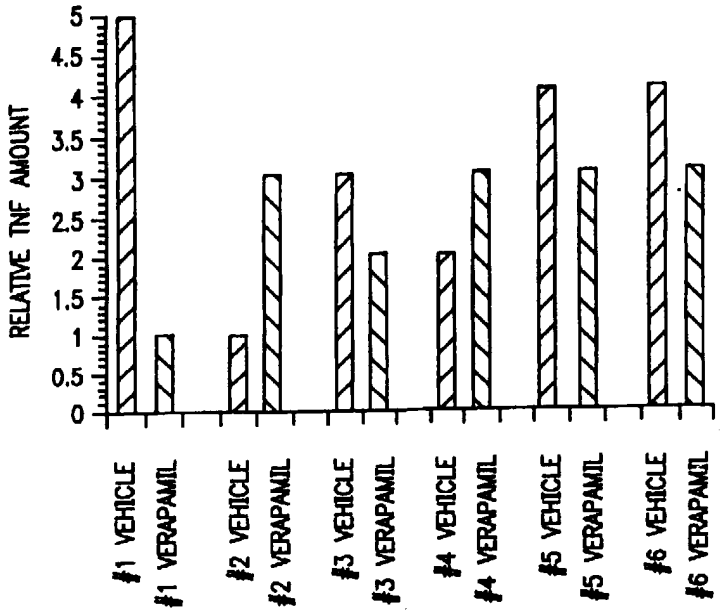

% PRE-CHALLENGE EAR THICKNESS
165
155
145
135
125
115
105
95
VEHICLE
AMILORIDE

FIG. 4


RELATIVE TNF AMOUNT
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
#1 VEHICLE
#1 VERAPAMIL
#2 VEHICLE
#2 VERAPAMIL
#3 VEHICLE
#3 VERAPAMIL
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#6 VEHICLE
#6 VERAPAMIL

FIG. 5

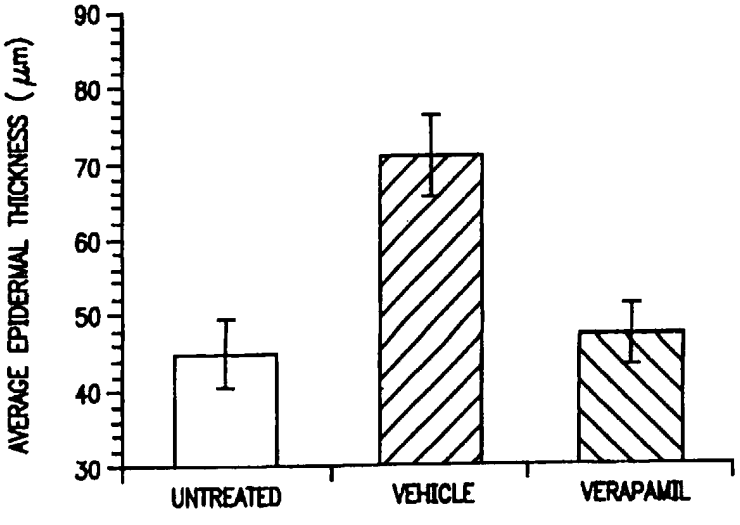

AVERAGE EPIDERMAL THICKNESS (μm)
90
80
70
60
50
40
30
UNTREATED
VEHICLE
VERAPAMIL

FIG. 6

Home : Diabetes A-Z List of Topics and Titles : Diabetic Neuropathies: The Nerve Damage of Diabetes

Also see:
Prevent Diabetes Problems: Keep Your Feet and Skin Healthy

Diabetic Neuropathies: The Nerve Damage of Diabetes

On this page:

Diabetic neuropathies are a family of nerve disorders caused by diabetes. People with diabetes can, over time, have damage to nerves throughout the body. Neuropathies lead to numbness and sometimes pain and weakness in the hands, arms, feet, and legs. Problems may also occur in every organ system, including the digestive tract, heart, and sex organs. People with diabetes can develop nerve problems at any time, but the longer a person has diabetes, the greater the risk.

An estimated 50 percent of those with diabetes have some form of neuropathy, but not all with neuropathy have symptoms. The highest rates of neuropathy are among people who have had the disease for at least 25 years.

Diabetic neuropathy also appears to be more common in people who have had problems controlling their blood glucose levels, in those with high levels of blood fat and blood pressure, in overweight people, and in people over the

age of 40. The most common type is peripheral neuropathy, also called distal symmetric neuropathy, which affects the arms and legs.

[Top]

Causes

The causes are probably different for different varieties of diabetic neuropathy. Researchers are studying the effect of glucose on nerves to find out exactly how prolonged exposure to high glucose causes neuropathy. Nerve damage is likely due to a combination of factors:

- metabolic factors, such as high blood glucose, long duration of diabetes, possibly low levels of insulin, and abnormal blood fat levels
- neurovascular factors, leading to damage to the blood vessels that carry oxygen and nutrients to the nerves
- autoimmune factors that cause inflammation in nerves
- mechanical injury to nerves, such as carpal tunnel syndrome
- inherited traits that increase susceptibility to nerve disease
- lifestyle factors such as smoking or alcohol use

[Top]

Symptoms

Symptoms depend on the type of neuropathy and which nerves are affected. Some people have no symptoms at all. For others, numbness, tingling, or pain in the feet is often the first sign. A person can experience both pain and numbness. Often, symptoms are minor at first, and since most nerve damage occurs over several years, mild cases may go unnoticed for a long time. Symptoms may involve the sensory or motor nervous system, as well as the involuntary (autonomic) nervous system. In some people, mainly those with focal neuropathy, the onset of pain may be sudden and severe.

Symptoms may include

- numbness, tingling, or pain in the toes, feet, legs, hands, arms, and fingers
- wasting of the muscles of the feet or hands
- indigestion, nausea, or vomiting
- diarrhea or constipation
- dizziness or faintness due to a drop in postural blood pressure
- problems with urination
- erectile dysfunction (impotence) or vaginal dryness
- weakness

In addition, the following symptoms are not due to neuropathy but nevertheless often accompany it:

- weight loss
- depression

[Top]

Types of Diabetic Neuropathy

Diabetic neuropathies can be classified as peripheral, autonomic, proximal, and focal. Each affects different parts of the body in different ways.

- Peripheral neuropathy causes either pain or loss of feeling in the toes, feet, legs, hands, and arms.
- Autonomic neuropathy causes changes in digestion, bowel and bladder function, sexual response, and perspiration. It can also affect the nerves that serve the heart and control blood pressure. Autonomic neuropathy can also cause hypoglycemia (low blood sugar) unawareness, a condition in which people no longer experience the warning signs of hypoglycemia.
- Proximal neuropathy causes pain in the thighs, hips, or buttocks and leads to weakness in the legs
- Focal neuropathy results in the sudden weakness of one nerve, or a group of nerves, causing muscle

weakness or pain. Any nerve in the body may be affected.

[Top]

Neuropathy Affects Nerves Throughout the Body

Peripheral Neuropathy

- toes
- feet
- legs
- hands
- arms

Autonomic Neuropathy

- heart and blood vessels
- digestive system
- urinary tract
- sex organs
- sweat glands
- eyes

Proximal Neuropathy

- thighs
- hips
- buttocks

Focal Neuropathy

- eyes
- facial muscles
- ears
- pelvis and lower back
- thighs
- abdomen

[Top]

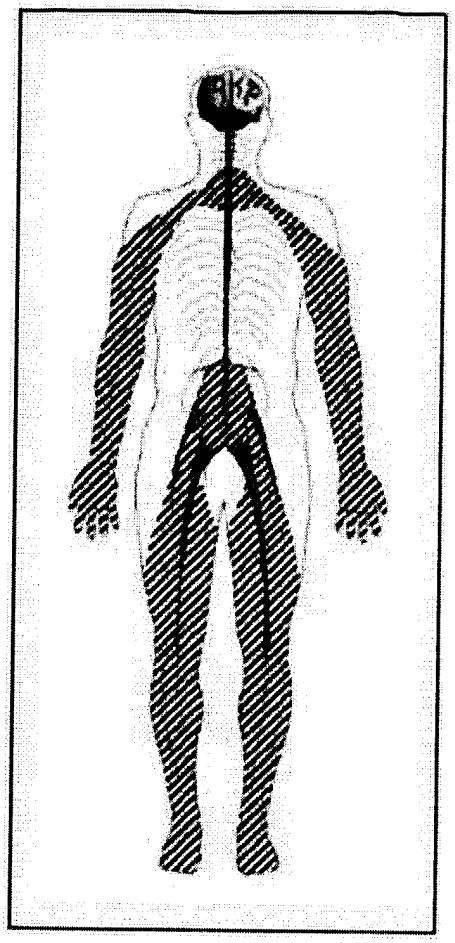
Peripheral Neuropathy

This type of neuropathy damages nerves in the arms and legs. The feet and legs are likely to be affected before the hands and arms. Many people with diabetes

have signs of neuropathy upon examination but have no symptoms at all. Symptoms of peripheral neuropathy may include

- numbness or insensitivity to pain or temperature
- a tingling, burning, or prickling sensation
- sharp pains or cramps
- extreme sensitivity to touch, even a light touch
- loss of balance and coordination

These symptoms are often worse at night.



Peripheral neuropathy affects the nerves in your arms, hands, legs, and feet.

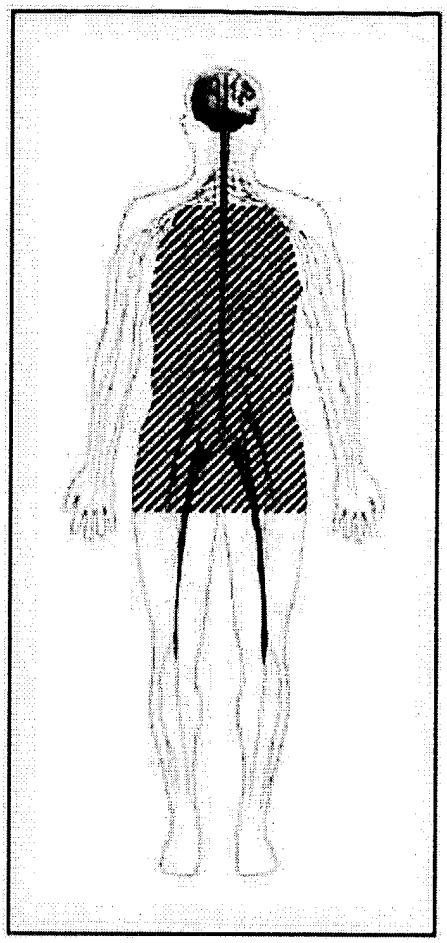
Peripheral neuropathy may also cause muscle weakness and loss of reflexes, especially at the ankle, leading to changes in gait (walking). Foot deformities, such as hammertoes and the collapse of the midfoot, may occur. Blisters and sores may appear on numb areas of the foot because pressure or injury goes unnoticed. If foot injuries are not treated promptly, the infection may spread to the bone, and the foot may then have to be amputated. Some experts estimate that half of all such amputations are preventable if minor problems are caught and treated in time.

[Top]

Autonomic Neuropathy

Autonomic neuropathy affects the nerves that control the heart, regulate blood pressure, and control blood glucose levels. It also affects other internal

organs, causing problems with digestion, respiratory function, urination, sexual response, and vision. In addition, the system that restores blood glucose levels to normal after a hypoglycemic episode may be affected, resulting in loss of the warning signs of hypoglycemia such as sweating and palpitations.



Autonomic neuropathy affects the nerves in your lungs, heart, stomach, intestines, bladder, and sex organs.

Unawareness of Hypoglycemia

Normally, symptoms such as shakiness occur as blood glucose levels drop below 70 mg/dL. In people with autonomic neuropathy, symptoms may not occur, making hypoglycemia difficult to recognize.

However, other problems can also cause hypoglycemia unawareness so this does not always indicate nerve damage.

Heart and Circulatory System

The heart and circulatory system are part of the cardiovascular system, which controls blood circulation. Damage to nerves in the cardiovascular system interferes with the body's ability to adjust blood pressure and heart rate. As a result, blood pressure may drop sharply after sitting or standing, causing a person to feel light-headed--or even to faint. Damage to the nerves that control heart rate can mean that it stays high, instead of rising and falling in response to normal body functions and exercise.

Digestive System

Nerve damage to the digestive system most commonly causes constipation. Damage can also cause the stomach to empty too slowly, a condition called gastroparesis. Severe gastroparesis can lead to persistent nausea and vomiting, bloating, and loss of appetite. Gastroparesis can make blood

glucose levels fluctuate widely as well, due to abnormal food digestion.

Nerve damage to the esophagus may make swallowing difficult, while nerve damage to the bowels can cause constipation alternating with frequent, uncontrolled diarrhea, especially at night. Problems with the digestive system may lead to weight loss.

Urinary Tract and Sex Organs

Autonomic neuropathy most often affects the organs that control urination and sexual function. Nerve damage can prevent the bladder from emptying completely, allowing bacteria to grow in the bladder and kidneys and causing urinary tract infections. When the nerves of the bladder are damaged, urinary incontinence may result because a person may not be able to sense when the bladder is full or control the muscles that release urine.

Neuropathy can also gradually decrease sexual response in men and women, although the sex drive is unchanged. A man may be unable to have erections or may reach sexual climax without ejaculating normally. A woman may have difficulty with lubrication, arousal, or orgasm.

Sweat Glands

Autonomic neuropathy can affect the nerves that control sweating. When nerve damage prevents the sweat glands from working properly, the body cannot regulate its temperature properly. Nerve damage can also cause profuse sweating at night or while eating.

Eyes

Finally, autonomic neuropathy can affect the pupils of the eyes, making them less responsive to changes in light. As a result, a person may not be able to see well when the light is turned on in a dark room or may have trouble driving at night.

[Top]

Proximal Neuropathy

Proximal neuropathy, sometimes called lumbosacral plexus neuropathy, femoral neuropathy, or diabetic amyotrophy, starts with pain in either the thighs, hips, buttocks, or legs,

usually on one side of the body. This type of neuropathy is more common in those with type 2 diabetes and in older people. It causes weakness in the legs, manifested by an inability to go from a sitting to a standing position without help. Treatment for weakness or pain is usually needed. The length of the recovery period varies, depending on the type of nerve damage.

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Focal Neuropathy

Occasionally, diabetic neuropathy appears suddenly and affects specific nerves, most often in the head, torso, or leg. Focal neuropathy may cause

- inability to focus the eye
- double vision
- aching behind one eye
- paralysis on one side of the face (Bell's palsy)
- severe pain in the lower back or pelvis
- pain in the front of a thigh
- pain in the chest, stomach, or flank
- pain on the outside of the shin or inside the foot
- chest or abdominal pain that is sometimes mistaken for heart disease, heart attack, or appendicitis

Focal neuropathy is painful and unpredictable and occurs most often in older people. However, it tends to improve by itself over weeks or months and does not cause long-term damage.

People with diabetes also tend to develop nerve compressions, also called entrapment syndromes. One of the most common is carpal tunnel syndrome, which causes numbness and tingling of the hand and sometimes muscle weakness or pain. Other nerves susceptible to entrapment may cause pain on the outside of the shin or the inside of the foot.

[Top]

Preventing Diabetic Neuropathy

The best way to prevent neuropathy is to keep your blood glucose levels as close to the normal range as possible. Maintaining safe blood glucose levels protects nerves throughout your body.

For additional information on preventing diabetes complications, including neuropathy, see the Prevent Diabetes Problems series, available from the National Diabetes Information Clearinghouse at 1-800-860-8747.

[Top]

Diagnosis

Neuropathy is diagnosed on the basis of symptoms and a physical exam. During the exam, the doctor may check blood pressure and heart rate, muscle strength, reflexes, and sensitivity to position, vibration, temperature, or a light touch.

The doctor may also do other tests to help determine the type and extent of nerve damage.

- A ***comprehensive foot exam*** assesses skin, circulation, and sensation. The test can be done during a routine office visit. To assess protective sensation or feeling in the foot, a nylon monofilament (similar to a bristle on a hairbrush) attached to a wand is used to touch the foot. Those who cannot sense pressure from the monofilament have lost protective sensation and are at risk for developing foot sores that may not heal properly. Other tests include checking reflexes and assessing vibration perception, which is more sensitive than touch pressure.

- ***Nerve conduction studies*** check the transmission of electrical current through a nerve. With this test, an image of the nerve conducting an electrical signal is projected onto a screen. Nerve impulses that seem slower or weaker than usual indicate possible damage. This test allows the doctor to assess the condition of all the nerves in the arms and legs.

- ***Electromyography (EMG)*** shows how well muscles respond to electrical signals transmitted by nearby nerves. The electrical activity of the muscle is displayed on a screen. A response that is slower or weaker than usual suggests damage to the nerve or

muscle. This test is often done at the same time as nerve conduction studies.

- ***Quantitative sensory testing (QST)*** uses the response to stimuli, such as pressure, vibration, and temperature, to check for neuropathy. QST is increasingly used to recognize sensation loss and excessive irritability of nerves.

- ***A check of heart rate variability*** shows how the heart responds to deep breathing and to changes in blood pressure and posture.

- ***Ultrasound*** uses sound waves to produce an image of internal organs. An ultrasound of the bladder and other parts of the urinary tract, for example, can show how these organs preserve a normal structure and whether the bladder empties completely after urination.

- ***Nerve or skin biopsy*** involves removing a sample of nerve or skin tissue for examination by microscope. This test is most often used in research settings.

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Treatment

The first step is to bring blood glucose levels within the normal range to prevent further nerve damage. Blood glucose monitoring, meal planning, exercise, and oral drugs or insulin injections are needed to control blood glucose levels. Although symptoms may get worse when blood glucose is first brought under control, over time, maintaining lower blood glucose levels helps lessen neuropathic symptoms. Importantly, good blood glucose control may also help prevent or delay the onset of further problems.

Additional treatment depends on the type of nerve problem and symptom, as described in the following sections.

[Top]

Foot Care

People with neuropathy need to take special care of their feet. The nerves to the feet are the longest in the body and are the ones most often affected by neuropathy. Loss of sensation in the feet means that sores or injuries may not be noticed and may become ulcerated or infected. Circulation

problems also increase the risk of foot ulcers.

More than half of all lower limb amputations in the United States occur in people with diabetes--86,000 amputations per year. Doctors estimate that nearly half of the amputations caused by neuropathy and poor circulation could have been prevented by careful foot care. Here are the steps to follow:

- Clean your feet daily, using warm--not hot--water and a mild soap. Avoid soaking your feet. Dry them with a soft towel; dry carefully between your toes.
- Inspect your feet and toes every day for cuts, blisters, redness, swelling, calluses, or other problems. Use a mirror (laying a mirror on the floor works well) or get help from someone else if you cannot see the bottoms of your feet. Notify your health care provider of any problems.
- Moisturize your feet with lotion, but avoid getting it between your toes.
- After a bath or shower, file corns and calluses gently with a pumice stone.
- Each week or when needed, cut your toenails to the shape of your toes and file the edges with an emery board.
- Always wear shoes or slippers to protect your feet from injuries. Prevent skin irritation by wearing thick, soft, seamless socks.
- Wear shoes that fit well and allow your toes to move. Break in new shoes gradually by wearing them for only an hour at a time at first.
- Before putting your shoes on, look them over carefully and feel the insides with your hand to make sure they have no tears, sharp edges, or objects in them that might injure your feet.
- If you need help taking care of your feet, make an appointment to see a foot doctor, also called a podiatrist.

For additional information on foot care, contact the National Diabetes Information Clearinghouse at 1-800-860-8747. Materials are also available at

http://ndep.nih.gov/materials/pubs/feet/feet.htm.

Pain Relief

To relieve pain, burning, tingling, or numbness, the doctor may suggest aspirin, acetaminophen, or nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen. (People with renal disease should use NSAIDs only under a doctor's supervision.) A topical cream called capsaicin is another option. Tricyclic antidepressant medications such as amitriptyline, imipramine, and nortriptyline, or anticonvulsant medications such as carbamazepine or gabapentin may relieve pain in some people. Codeine may be prescribed for a short time to relieve severe pain. Also, mexiletine, used to regulate heartbeat, has been effective in treating pain in several clinical trials.

Other pain treatments include transcutaneous electronic nerve stimulation (TENS), which uses small amounts of electricity to block pain signals, as well as hypnosis, relaxation training, biofeedback, and acupuncture. Walking regularly or using elastic stockings may also help leg pain.

Gastrointestinal Problems

To relieve mild symptoms of gastroparesis--indigestion, belching, nausea, or vomiting--doctors suggest eating small, frequent meals, avoiding fats, and eating less fiber. When symptoms are severe, the doctor may prescribe erythromycin to speed digestion, metoclopramide to speed digestion and help relieve nausea, or other drugs to help regulate digestion or reduce stomach acid secretion.

To relieve diarrhea or other bowel problems, the doctor may prescribe an antibiotic such as tetracycline, or other medications as appropriate.

Dizziness and Weakness

Sitting or standing slowly may help prevent the light-headedness, dizziness, or fainting associated with blood pressure and circulation problems. Raising the head of the bed or wearing elastic stockings may also help. Some people may benefit from increased salt in the diet and treatment with salt-retaining hormones. Others may benefit from high blood pressure medications. Physical therapy can help when muscle weakness or loss of coordination is a problem.

Urinary and Sexual Problems

To clear up a urinary tract infection, the doctor will probably prescribe an antibiotic. Drinking plenty of fluids will help prevent another infection. People who have incontinence should try to urinate at regular intervals (every 3 hours, for example) since they may not be able to tell when their bladder is full.

To treat erectile dysfunction in men, the doctor will first do tests to rule out a hormonal cause. Several methods are available to treat erectile dysfunction caused by neuropathy, including taking oral drugs, using a mechanical vacuum device, or injecting a drug called a vasodilator into the penis before sex. The vacuum and vasodilator raise blood flow to the penis, making it easier to have and maintain an erection. Another option is to surgically implant an inflatable or semirigid device in the penis. A constriction ring or penile sling may be helpful.

Vaginal lubricants may be useful for women when neuropathy causes vaginal dryness. To treat problems with arousal and orgasm, the doctor may refer the woman to a gynecologist.

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Points to Remember

- Diabetic neuropathies are nerve disorders caused by many of the abnormalities common to diabetes, such as high blood glucose.
- Neuropathy can affect nerves throughout the body, causing numbness and sometimes pain in the hands, arms, feet, or legs, and problems with the digestive tract, heart, and sex organs.
- Treatment first involves bringing blood glucose levels within the normal range. Good blood glucose control may help prevent or delay the onset of further problems.
- Foot care is another important part of treatment. People with neuropathy need to inspect their feet daily for any injuries. Untreated injuries increase the risk of infected foot sores and amputation.
- Treatment also includes pain relief and other

medications as needed, depending on the type of nerve damage.

- Smoking significantly increases the risk of foot problems and amputation. If you smoke, ask your health care provider for help in quitting.

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Hope Through Research

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the National Institute of Neurological Disorders and Stroke (NINDS) conduct and support research to help people with diabetes, including studies related to diabetic neuropathy. A complete listing of clinical research studies can be found at http://ClinicalTrials.gov.

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For More Information

For more information, contact the following organizations:

American Diabetes Association
National Service Center
1701 North Beauregard Street
Alexandria, VA 22311
Phone: 1-800-232-3472 or 1-800-DIABETES (1-800-342-2383) Fax: (703) 549-6995
Email: customerservice@diabetes.org
Internet: www.diabetes.org

American Foundation for Urologic Disease
1128 North Charles Street
Baltimore, MD 21201
Phone: 1-800-242-2383 or (410) 468-1800
Email: admin@afud.org
Internet: www.afud.org

American Podiatric Medical Association
9312 Old Georgetown Road
Bethesda, MD 20814-1698
Phone: 1-800-FOOT-CARE
(1-800-366-8227) or (301) 571-9200
Fax: (301) 530-2752
Email: askapma@apma.org
Internet: www.apma.org

Centers for Disease Control and Prevention
National Center for Chronic Disease
Prevention and Health Promotion
Division of Diabetes Translation
Mail Stop K-10
4770 Buford Highway, NE.
Atlanta, GA 30341-3717
Phone: 1-800-CDC-DIAB
(1-800-232-3422)
Fax: (301) 562-1050
Email: diabetes@cdc.gov
Internet: www.cdc.gov/diabetes

Juvenile Diabetes Research Foundation International
120 Wall Street, 19th floor
New York, NY 10005
Phone: 1-800-533-2873 or (212) 785-9500
Fax: (212) 785-9595
Email: info@jdrf.org
Internet: www.jdrf.org

Lower Extremity Amputation Prevention Program
HRSA/BPH/DPSP
4350 East-West Highway, 9th floor
Bethesda, MD 20814
Phone: 1-888-275-4772
Internet: www.bphc.hrsa.gov/leap

National Diabetes Education Program
1 Diabetes Way
Bethesda, MD 20892-3600
Phone: 1-800-438-5383
Internet: http://ndep.nih.gov

National Digestive Diseases Information Clearinghouse
2 Information Way
Bethesda, MD 20892-3570
Phone: 1-800-891-5389 or (301) 654-3810
Fax: (301) 907-8906
Email: nddic@info.niddk.nih.gov
Internet: www.niddk.nih.gov/health/digest/nddic.htm

National Heart, Lung, and Blood Institute Information Center
P.O. Box 30105
Bethesda, MD 20824-0105
Phone: (301) 592-8573
Fax: (301) 592-8563
Email: NHLBIinfo@rover.nhlbi.nih.gov
Internet: www.nhlbi.nih.gov/health/infoctr

National Institute of Neurological Disorders and Stroke
P.O. Box 5801
Bethesda, MD 20824
Phone: 1-800-352-9424
Internet: www.ninds.nih.gov

National Kidney and Urologic Diseases Information Clearinghouse
3 Information Way
Bethesda, MD 20892-3580
Phone: 1-800-891-5390 or (301) 654-4415
Fax: (301) 907-8906
Email: nkudic@info.niddk.nih.gov
Internet: www.niddk.nih.gov/health/kidney/nkudic.htm

Pedorthic Footwear Association
7150 Columbia Gateway Drive, Suite G
Columbia, MD 21046-1151
Phone: 1-800-673-8447 or (410) 381-7278
Fax: (410) 381-1167
Internet: www.pedorthics.org

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National Diabetes Information Clearinghouse

1 Information Way
Bethesda, MD 20892-3560
Email: ndic@info.niddk.nih.gov

The National Diabetes Information Clearinghouse (NDIC) is a service of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). The NIDDK is part of the National Institutes of Health under the U.S. Department of Health and Human Services. Established in 1978, the clearinghouse provides information about diabetes to people with diabetes and to their families, health care professionals, and the public. NDIC answers inquiries, develops and distributes publications, and works closely with professional and patient organizations and Government agencies to coordinate resources about diabetes.

This fact sheet was reviewed by Peter J. Dyck, M.D., Peripheral Neuropathy Research Center, Mayo Clinic Rochester, Rochester, MN; Eva L. Feldman, M.D., Ph.D., Department of Neurology, University of Michigan, Ann Arbor, MI; and Aaron I. Vinik, M.D., The Diabetes Research Institute, Eastern Virginia Medical School, Norfolk, VA.

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Inflammation Blocks Impact of Heart Healthy Diets for Some

posted 07/28/03

Results of a Johns Hopkins study suggest that natural chemicals released in the body as a result of chronic **inflammation** may underpin the failure of low-fat, so-called heart healthy diets to actually reduce cholesterol and heart disease risk in some people.

According to the study's results, published in the July 15 issue of Circulation, measuring circulating blood levels of C-reactive protein -- a marker of **inflammation** already linked to increased risk of heart disease -- may predict who might benefit from a reduced-fat, low-cholesterol diet and who might not.

For the study, a team led by Thomas "Tate" P. Erlinger, M.D., M.P.H., assistant professor of medicine, tracked 100 subjects with elevated CRP levels following a reduced-fat, low-cholesterol diet for 12 weeks. They found that overall, this group had less of a reduction in total cholesterol and low-density lipoprotein (LDL) or "bad" cholesterol levels. Subjects also had a greater increase in triglycerides compared with another group on the same diet but with lower CRP levels.

Subjects with lower CRP readings at the start of the study (less than 2.37 milligrams per liter) had a nearly 10 percent drop in total cholesterol and nearly 12 percent reduction in LDL cholesterol. Their triglycerides were not affected. In those with higher CRP (more than 2.37 mg/L), total and LDL cholesterol were lowered by only 3 percent each, while triglycerides rose by 19 percent.

Erlinger cautions that the study sample was small and did not examine the impact of weight loss on CRP levels.

"An important implication of our findings is that we may be able to use CRP testing to distinguish those who are likely to have a favorable response to a reduced-fat, low-cholesterol diet from those who will not respond well," says Erlinger. "It may also help explain why different people on the same diet may have widely varying results. It's too early for broad recommendations, but additional research in this area could help physicians tailor diets for specific patients."

While causes of **inflammation** vary, the condition itself has already been linked to several cardiovascular risk factors including hypertension, **diabetes** and elevated triglycerides. CRP has recently been identified -- along with cigarette smoking and obesity -- as a risk factor for cardiovascular disease.

The 100 healthy adults in the study had an average age of 52 and already were participating in the national Dietary Approaches to Stop Hypertension-Sodium (DASH-Sodium) trial.

The Hopkins team took blood samples from each participant at the study's start to measure CRP, cholesterol and triglycerides. After two weeks on a control diet of 37 percent total fat and 16 percent saturated fat, participants were assigned to continue to follow either the

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control diet or the DASH diet, which calls for 27 percent total fat and 6 percent saturated fat, for 12 weeks.

The study was supported by grants from the National Institutes of Health, the National Heart, Lung and Blood Institute and the General Clinical Research Center at Johns Hopkins. Co-authors were Edgar R. Miller III, M.D., Ph.D.; Jeanne Charleston, R.N.; and Lawrence J. Appel, M.D., M.P.H.

Erlinger, Thomas P. et al, "**Inflammation** Modifies the Effects of a Reduced Fat, Low Cholesterol Diet on Lipids: Results from the DASH-Sodium Trial," Circulation, July 15, 2003; Vol. 108, pages 150-154.

Links:

- Johns Hopkins' Welch Center for Prevention, Epidemiology and Clinical Research
  http://www.med.jhu.edu/welchcenter/
- Circulation
  http://circ.ahajournals.org/
- Information on the DASH diet
  http://www.nhlbi.nih.gov/health/public/heart/hbp/dash/

Source: The Diabetic News: Johns Hopkins.

July News Article Index

Date of last update: 04/01/04

To contact Webmaster: webmaster@defeatdiabetes.org

1: Ann Pharmacother. 1995 Jul-Aug;29(7-8):769-77.

Peripheral diabetic neuropathy: current concepts in treatment.

Calissi PT, Jaber LA.

Pharmacy Department, St Paul's Hospital (Grey Nuns), Saskatoon, Saskatchewan.

OBJECTIVE: To review pathophysiology and current concepts in the treatment of diabetic peripheral neuropathy (PN). DATA SOURCES: References were identified through a MEDLINE search of the English-language literature from 1976 through 1994. Additional references were obtained from reference lists of articles identified through the search. STUDY SELECTION AND DATA EXTRACTION: All articles were considered for possible inclusion in the review. Clinical trials that involved an adequate number of patients and review articles were selected. Information from articles that was judged by the authors to be significant was selected for discussion. DATA SYNTHESIS: PN affects 5-50% of people with diabetes in the US and most commonly is characterized by tingling or burning sensations, particularly in the calves, ankles, and feet, with a loss of vibratory sense. Treatment of PN, for the most part, has been unsatisfactory. Therapy has been directed toward either improving nerve function or alleviating symptoms of PN, including pain and paresthesia. Glycemic control may slow the progression of PN. Hyperglycemia also is associated with decreased pain threshold in patients with diabetes mellitus. The aldose reductase inhibitors, particularly tolrestat, have been shown to improve objective and subjective neurologic function. Pain or paresthesia has been treated effectively with antidepressants, lidocaine, mexiletine, and capsaicin. The anticonvulsants phenytoin and carbamazepine may be effective, but are associated with a greater degree of adverse effects. Experimental treatments, such as gamma-linolenic acid, gangliosides, uridine,

and the corticotropin4-9 analog ORG 2766, have been effective in improving neurologic function. CONCLUSIONS: Treatment of PN remains unsatisfactory. Therapy should be directed toward prevention with glycemic control and symptomatic treatment of existing PN.

Publication Types:

- Review
- Review, Tutorial

MeSH Terms:

- Aldehyde Reductase/antagonists & inhibitors
- Aldehyde Reductase/therapeutic use
- Anoxia/complications
- Antidepressive Agents/therapeutic use
- Blood Glucose/analysis
- Clinical Trials
- Diabetes Mellitus, Type I/drug therapy
- Diabetic Neuropathies/drug therapy*
- Diabetic Neuropathies/physiopathology
- Diabetic Neuropathies/prevention & control
- Human
- Hyperglycemia/prevention & control
- Insulin/therapeutic use

Substances:

- Antidepressive Agents
- Blood Glucose
- Insulin
- Aldehyde Reductase

PMID: 8520095 [PubMed - indexed for MEDLINE]

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